QUALITY OF LIFE POST-THYROIDECTOMY IN BENIGN GOITRES: A PROSPECTIVE OBSERVATIONAL STUDY

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF M.S. GENERAL SURGERY BRANCH I EXAMINATION OF THE TAMIL NADU DR. M.G.R. UNIVERSITY, CHENNAI TO BE HELD IN MAY 2019

CERTIFICATE

This is to certify that the dissertation titled “Quality of life post Thyroidectomy in benign goiters” is a bonafide work of Dr.Swarna Azaria, carried out under our guidance towards partial fulfillment of M.S General Surgery Branch 1 examination of the Tamil Nadu Dr.M.G.R University, Chennai to be held in 2019.

Vellore

October 2018

Dr.Sukria Nayak

Professor and Head of Department

Department of General Surgery

Christian Medical College

Vellore

Tamil Nadu - 632004

Dr.Anna B Pulimood

Principal

Christian Medical College

Vellore

Tamil Nadu - 632004

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Vellore

October 2018

Dr.Pranay Gaikwad

Professor and Head

General Surgery 1

Christian Medical College

Vellore

Tamil Nadu – 632004

Dr.Deepak Thomas Abraham

Professor and Head

Endocrine Surgery

Christian Medical College

Vellore

Tamil Nadu - 632004

DECLARATION CERTIFICATE

This is to certify that the dissertation titled “Quality of life post Thyroidectomy in benign goiters” submitted by me towards partial fulfillment of M.S General Surgery Branch 1 examination of the Tamil Nadu Dr.M.G.R University, Chennai to be held in 2019,comprises only my original work and due acknowledgement has been made in text to all the material used.

Vellore

October 2018

Dr.Swarna Azaria

Post graduate registrar

Department of General Surgery

Christian Medical College

Vellore

Tamil Nadu - 632004

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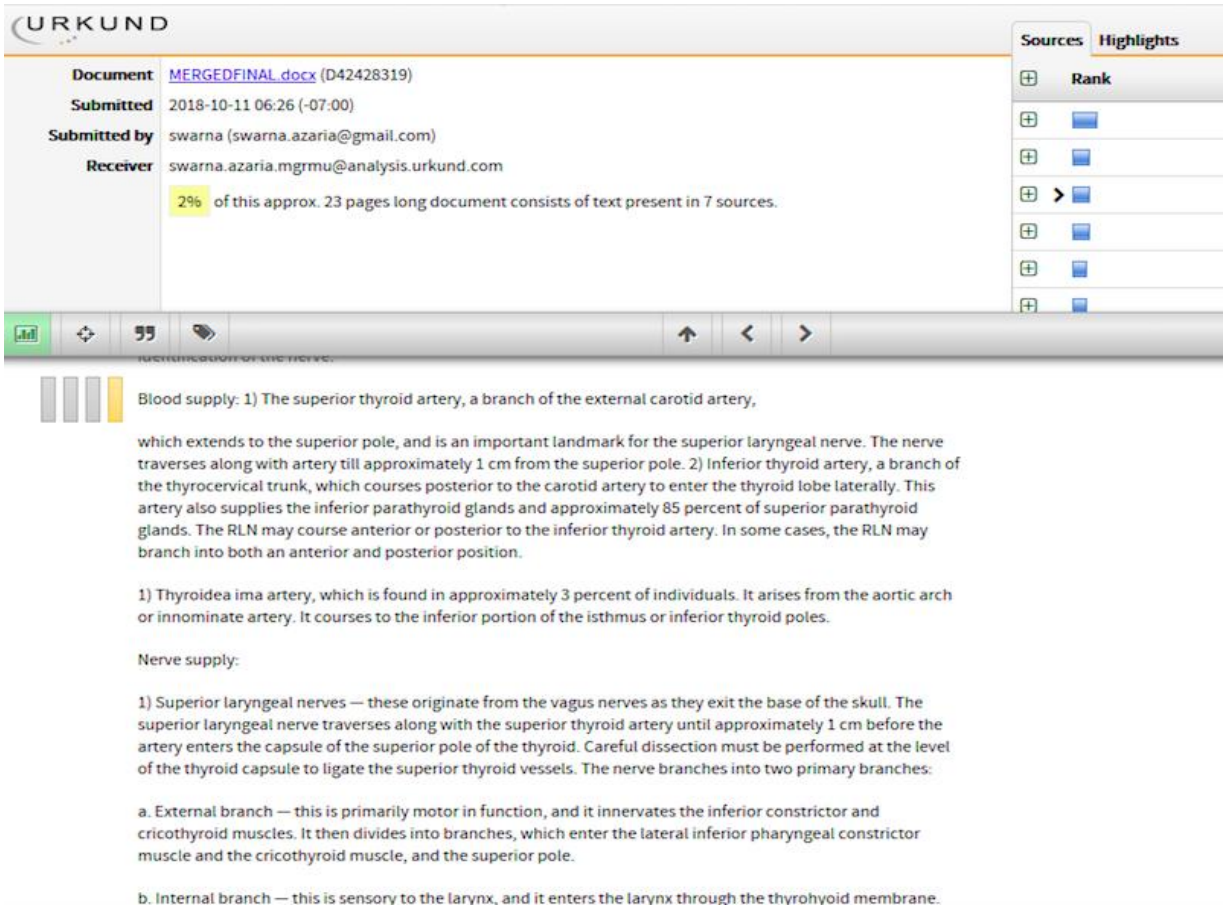

Dr.Pranay Gaikwad

Professor and Head

General Surgery 1

Christian Medical College

Vellore

Tamil Nadu – 632004

Dr.Deepak Thomas Abraham

Professor and Head

Endocrine Surgery

Christian Medical College

Vellore

Tamil Nadu - 632004

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I will be deeply grateful forever to God, my constant supporter and my sustenance.

My biggest encouragers have been my family – Dr.Ashvin J Paul, Col. J. Azaria and Chitra Azaria, Dr. Jayaraj Azaria, Dr.Cheryl Jayaraj and baby Prerit Jayaraj. Their support and love have constantly lifted and inspired me.

My mentors who are surely the giants on whose shoulders I stand - Dr.Deepak Abraham, Dr. Anish Cherian,and Dr.Pranay Gaikwad, who have gone the extra mile on more than one occasion, and whose wonderful effort has been translated into the pages below. Their professional expertise and research driven minds have steadily motivated me. I would also like to thank Dr.Shawn Thomas for his cheerful contribution to this study.

Torquil Watt, the developer of the ThyPRO 39 questionnaire, has been very kind to allow us to use his research tool and in collaborating with us.

I wish to thank my statistician, Mrs. Gauri, who was very instrumental to this study.

Last but not the least; I would like to extend my heartfelt gratitude to my patients, who were willing to contribute to the field of science cheerfully despite their suffering.

IRB APPROVAL

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Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

December 13, 2016.

Dr. Swarna Azaria,
PG Registrar
Department of General Surgery,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Quality of life post Thyroidectomy in benign goiters
Swarna Azaria, Emp. No: 29577, PG Registrar, Dr. John C Muthusami, Emp. no- 12899, Professor and Head, Dr. Deepak Abraham, Emp. No: 20130, Prof & Head, Dr. Cecil Thomas, Emp. No:32376, Dr. Vasanth Mark Samuel, Emp. No: 33291, Department of General Surgery, Dr. Paul MJ, Emp. No: 14395, Dr. Anish Jacob Cherian, Emp. No: 28558, Dr. K. Ravikumar, Emp. No: 80046, Dr. Prasanna Samuel, Emp. No: 31654, Lecturer, Dept. of Biostatistics,

Ref: IRB Min. No. 10440 dated 05.12.2016

Dear Dr. Swarna Azaria,

The Institutional Review Board **(Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Quality of life post Thyroidectomy in benign goiters" on December 05th 2016. I am quoting below the minutes of the meeting.

The Committee raises the following queries:

1. Have you tried this questionnaire in a few patients
2. Are you systematically look at hypocalcemia and hypothyroidism post op since it will affect functional status
3. Sample size is based on which study – please quote

Drs. Swarna Azaria and Deepak Abraham were present during the presentation of the proposal and satisfactorily responded to the queries raised by the Members. After discussion, it was resolved to **ACCEPT the proposal after receiving the suggested modifications and answers to the queries.**

1 of 2

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.
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Note: 1. Kindly HIGHLIGHT the modifications in the revised proposal.
2. Keep a covering letter and point out the answer to the queries.
3. Reply to the queries should be submitted within 3 months duration from the time of the thesis/ protocol presentation, if not the thesis/protocol have to be resubmitted to the IRB.
4. The checklist has to be sent along with the answers to queries.

Email the details to research@cmcvellore.ac.in and send a hard copy through internal dispatch to Dr. Biju George, Addl. Vice-Principal (Research), Principal's Office, CMC.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board.

Dr. BIJU GEORGE
MBBS, MD, DM
SECRETARY - ETHICS COMMITTEE
Institutional Review Board
Christian Medical College, Vellore - 632 002.

Cc: Dr. John C Muthusami, Department of General Surgery, CMC Vellore.

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Chairperson, Research Committee & Principal

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Additional Vice-Principal (Research)

April 04, 2017

Dr. Swarna Azaria,
PG Registrar,
Department of General Surgery,
Christian Medical College,
Vellore - 632 004.

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Quality of life post Thyroidectomy in benign goiters
Swarna Azaria, Emp. No: 29577, PG Registrar, Dr. John C Muthusami, Emp. no- 12899, Professor and Head, Dr. Deepak Abraham, Emp. No: 20130, Prof & Head, Dr. Cecil Thomas, Emp. No:32376, Dr. Vasanth Mark Samuel, Emp. No: 33291, Department of General Surgery, Dr. Paul MJ, Emp. No: 14395, Dr. Anish Jacob Cherian, Emp. No: 28558, Dr. K. Ravikumar, Emp. No: 80046, Dr. Prasanna Samuel, Emp. No: 31654, Lecturer, Dept. of Biostatistics.

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Dear Dr. Swarna Azaria,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS, MD, DM
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. John C Muthusami, Dept. of General Surgery, CMC, Vellore

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Secretary, Ethics Committee, IRB
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Ref: IRB Min No: 10440 [OBSERVE] dated 05.12.2016

Dear Dr. Swarna Azaria,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Quality of life post Thyroidectomy in benign goiters" on December 05th 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Data Collection Sheet
3. Patient Information sheet and Consent Form (English, Bengali, Hindi)
4. Cvs of Drs. Ashish, Cecil, Deepak, John C Muthusami, M J Paul, Ravikumar, Swarna, Vasanth.
5. No. of documents 1- 4

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on December 05th 2016 in the BRTC Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB, Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Dr. Rekha Pai	BSc, MSc, PhD	Associate Professor, Pathology, CMC, Vellore	Internal,Basic Medical Scientist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Simon Pavamani	MBBS, MD	Professor, Radiotherapy, CMC, Vellore	Internal, Clinician
Dr. Rajesh Kannangai	MD, PhD.	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician

Dr. B.J. Prashantham, M.A., M.A., Dr.Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee,

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Santhanam Sridhar	MBBS, DCH, DNB	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Quality of life post Thyroidectomy in benign goiters" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:

A sum of 4,500/- INR (Rupees Four thousand Five hundred Only) will be granted for 12 months.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS, MD, DM,
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

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1. Introduction

A goitre is defined as a visibly enlarged thyroid gland. With progressive growth, direct pressure effects like hoarseness of voice, dysphagia and dyspnea can occur. Hormonal dysfunction affecting the thyroid gland also needs therapeutic intervention. Patients with benign goitres without these symptoms may undergo surgical intervention because of cosmetic disfigurement. However, this is often deferred due to disfigurement of the intervention or a fear of the complications of the intervention. Goitres also can be as a result of malignancy, which needs surgical intervention in most patients. Such effects are sometimes distressing and often the precipitating factor in seeking treatment.

However, benign thyroid diseases encompass a large spectrum of conditions that are chronic and subtle in nature without obvious pressure symptoms, hormonal dysfunction or features of malignancy. There are symptoms that cause subconscious disruption of good quality of life but are never dramatic enough to be able to pin them down to the thyroid disease. Another matter of great interest is that patients who are devoid of thyroid dysfunction and report to the outpatient department with no other complaints except for the goitres also have reported a general impaired quality of life on health related quality of life assessment(1).

1.1 Intervention for benign goitres

There are various options for management of benign goitres. Thyroidectomy is the most commonly performed endocrine operation worldwide. The other modalities include radio - iodine ablation for malignancy, anti thyroid medications for hyperthyroidism and thyroid hormone replacement for hypothyroidism. A vast number of patients devoid of hormonal

dysfunction also refuse thyroidectomy unless they have pressure effects such as dysphagia, dyspnoea or dysphonia. So a majority of patients choose conservative management, and continue living their daily lives with impairment of physical, mental, social, or optimal functioning without being aware of the incriminating cause.

1.2 Surgical Intervention

Operative management remains the most chosen option of these, mainly because of removal of a bothersome neck swelling with added benefits of improvement in hormonal dysfunction or pressure symptoms. The advantage of having a definite histopathological diagnosis is also an attraction as the lurking fear of malignancy can often be put to rest.

However, patients post thyroidectomy sometimes return to the outpatient department with unsatisfying issues like cosmesis or more fatigue after the operation. For a benign disease that is offered thyroidectomy, post-operative impairment of quality of life is a growing concern. Are we indeed offering the best modality with operative intervention?

1.3 The need for quality of life studies

The need for assessment of quality of life in benign goitres arose considering the vague ambiguity regarding its treatment modalities. Most international studies have paid attention to impairment in quality of life in thyroid malignancies and the impact of surgery on quality of life subsequently(1). Very few studies have studied the impact of benign goitres on quality of life, mainly due to lack of validated questionnaires. In our tertiary care set up, with a high volume of patients with thyroid diseases, during casual outpatient visits, few patients have complaints post thyroidectomy for benign goitres. Issues regarding cosmesis and such are subtle issues - which have been observed post operatively. The results of this study would help clinicians in realising

the significance of benign goitres on a patient's life, besides shedding light into the broad ambiguity regarding its treatment. The general popular notion that there is an improvement of quality of life in all patients after might be in for a surprise. It is possible that a fresh take on offering the best treatment for such patients might even exclude surgery.

2. Aims and objectives of the study

2.1 Aim of the study

To assess the Quality of life post Thyroidectomy in patients with goitres

2.2 Primary objectives:

- To assess the impact of Thyroidectomy on QOL in patients with benign goitres using the ThyPRO 39 questionnaire

2.3 Secondary objectives:

To assess the significance of factors affecting the outcome such as:

- Specimen weight and dimension
- Duration of symptoms
- Functional status
- Post operative hypocalcaemia
- Pathology

3. Literature review

3.1 Global disease burden

The prevalence of thyroid disorders is so significant that the burden faced by the world has reached epidemic proportions. An estimated 200 million individuals worldwide have a thyroid disorder. Almost one-third of the world's population lives in areas of iodine deficiency. The prevalence of goitre in areas of severe iodine deficiency can be as high as 80 % (2). Benign thyroid diseases constitute one such group of thyroid diseases, which may go undiagnosed for many years.

In India, a large cross sectional epidemiological multi-centric study done in 2011 revealed prevalence of hypothyroidism in the study population of eight major cities was 10.95%, of which 3.47% were previously undetected (3) . This implied that nearly one third of patients suffering from hypothyroidism remained undiagnosed and hence untreated, bearing with an impaired quality of life with its various implications on productivity and social standing.

Another Indian study done in 2012, reported clinical goitre in 9.6% of the study population, with subclinical hypothyroidism being the commonest entity encountered affecting 19.3 % (4). These figures throw light on a disease of a large scale, impacting many lives. For a disease that is subtle and not overly dramatic in its presentation most of the times, we have to understand the magnitude of the impact it can have on a daily basis. This, in turn, makes us wonder about the implications of this disease on quality of life by its mere presence.

3.2 Thyroidectomy most common endocrine operation worldwide

Thyroidectomy remains the most common endocrine operation being performed worldwide (5). The proportion of cases done by high volume centres and high volume surgeons has shown exponential growth over the decades (6). The various indications for thyroidectomy being:

1) Hormonal dysfunction
2) Pressure effects
3) Retrosternal extension
4) Risk of malignancy
5) Proven malignancy
6) Cosmesis

3.3 Historical approach to thyroid disease

The thyroid gland and its diseases are one of the oldest recognized, described, and deeply pondered upon entity in comparison to other conditions. There is literary proof of this in ancient Indian, Egyptian, and Greek medicine, not to forget Chinese and Byzantine articles. References to goitre have been dated as early as 2700 BC, in an era in which this widely prevalent disease with lack of knowledge of the cause and possible cure had caused much confusion and speculation (7).

It is interesting to note that thyroid diseases had already been subdivided into three subsets of hypothyroidism, hyperthyroidism, and thyroglossal cysts and had been described in extensive detail in India ayurvedic texts, with good correlation to what was described much later in modern medicine. Eminent personalities like Leonardo da Vinci's anatomical diagram of the exact location of the thyroid gland in 1511 and the joint description by Hippocrates and Plato in Greek literature also give a hint of the enormity of the disease in that era.

The evolution of thyroid disease can also be interpreted in the context of what was offered to treat these conditions over the ages.

As early as 1600 BC, Chinese physicians used to treat goitres. Byzantine physicians had experimented with substances like copper, sulphur and other chemical salts for the same (7).

The operative management of the thyroid gland has also seen many seasons through the ages. The history of thyroidectomy has a glorious past. The first described operation was performed by Albucasis in 952 AD, when he had described removal of a large goitre (8). The first partial thyroidectomy was described in 1791 by Pierre Joseph Desault, which was a landmark achievement.

However, the evolution saw many dry periods and downfalls as well. Due to the high mortality rate at that point of time due to causes like haemorrhage, hospital acquired gangrene, air embolism, etc, thyroid operations were even banned by the French Academy of Medicine in the 1850 (8).

With the advent of anaesthesia, improved antibiotic prophylaxis and better haemostatic techniques, thyroid surgery made its comeback. Theodore Kocher and Billroth did many inspiring thyroidectomies, with declining mortality rates. Kocher was awarded the Nobel Prize in 1909 for his illustrious work on thyroid surgery (8).

Surgeons had still continued to operate only on non-toxic goitres, as operating on toxic goitres was considered a catastrophic decision then. Plummer had done a landmark series of 600 thyroidectomies on toxic goitres with usage of Lugol's iodine preoperatively.

The next era saw the advent of non-operative advancements like the introduction of radioactive iodine into clinical practice in 1942. Soon after, important drugs like Thiouracil and Propranolol came into the market for toxic goitres.

The treatment of thyroid diseases has come a long way further from then.

3.4 Modern approach to the treatment of thyroid diseases

The current approach to diagnosis and treatment of thyroid disease has stemmed from many years of scientific work on understanding the roots of the disease. Like for instance the studies done to establish the embryological origin of the gland led to the discovery of thyroid rests. Thyroidectomy as of age includes removal of thyroid rests to offer curative treatment. Another example, is-understanding the complex physiology of the thyroid gland in the hypothalamic pituitary axis, due to which anti thyroid and thyroid replacement drugs have been substantiated.

To fully comprehend the importance of thyroidectomy, and the impact of the operation on various domains of life, the embryology, pathology, physiology and steps of thyroidectomy have been dealt with briefly in a sequential manner.

3.5 Embryology of Thyroid

The development of the thyroid as the first endocrine gland in the foetus depicts its importance. It starts around the latter end of the third week to early fourth week of gestation.

It originates at the foramen cecum. The medial thyroid analage is formed by thickening of the endoderm cells in the floor of the pharyngeal analage. During its descent, the analage remains connected to the foramen cecum via a tubular structure called as the thyroglossal duct. The

paired lateral analages originate from the fourth branchial pouch and fuse with the median analage at the fifth week of gestation.

These lateral analages are neuroectodermal in origin, called as ultimobranchial bodies, which come to lie in the superoposterior region of the gland. These provide the calcitonin producing parafollicular cells or C cells.

Lastly, folliculogenesis occurs, along with functional cell differentiation and thyroglobulin synthesis. Thyroid follicles are initially apparent by eight weeks of gestation. Endogenous hormone production is usually seen after eleven weeks of gestation.

3.6 Pathology

The microscopic picture of the thyroid is the visualization of lobules that contain usually 20 to 40 follicles each. The follicles are spherical in shape, lined by cuboidal epithelial cells. There is a central store of colloid secreted from the epithelial cells in each follicle. The secretion of colloid occurs under the influence of TSH. C cells or parafollicular cells is the other group of secretory cells, which secrete the hormone calcitonin. These cells are located in the upper poles of thyroid lobes.

3.7 Anatomy of Thyroid

The thyroid gland is a highly vascular organ lying in the midline of the neck, weighing 15 – 20 grams in an average adult. The trachea and oesophagus lie medial to it, and the carotid sheath lies laterally. It encircles the anterolateral portion of the trachea. The strap muscles and sternocleidomastoid muscle border it anteriorly and laterally.

The gland has two main lobes connected by a narrow band called the isthmus. Each lobe has a superior and inferior pole. The extent of each lobe is - from the isthmus superiorly to the mid-thyroid cartilage.

The isthmus overlies the second and third tracheal rings.

The pyramidal gland is a part of the gland that extends from the isthmus to the hyoid bone. Occasionally, a thyroglossal duct cyst may be found in this extension to the hyoid.

On the posterior aspect of each lobe lies the tubercle of Zuckerkandl. This is an important surgical landmark as the recurrent laryngeal nerve (RLN) usually traverses posterior to this. During dissection it is essential to medially rotate the tubercle to help in identification of the nerve.

Blood supply:

1) The superior thyroid artery, a branch of the external carotid artery, which extends to the superior pole, and is an important landmark for the superior laryngeal nerve. The nerve traverses along with artery till approximately 1 cm from the superior pole.
2) Inferior thyroid artery, a branch of the thyrocervical trunk, which courses posterior to the carotid artery to enter the thyroid lobe laterally. This artery also supplies the inferior parathyroid glands and approximately 85 percent of superior parathyroid glands. The RLN may course anterior or posterior to the inferior thyroid artery. In some cases, the RLN may branch into both an anterior and posterior position.
1) Thyroidea ima artery, which is found in approximately 3 percent of individuals. It arises from the aortic arch or innominate artery. It courses to the inferior portion of the isthmus or inferior thyroid poles.

Nerve supply:

1) Superior laryngeal nerves — these originate from the vagus nerves as they exit the base of the skull. The superior laryngeal nerve traverses along with the superior thyroid artery until approximately 1 cm before the artery enters the capsule of the superior pole of the thyroid. Careful dissection must be performed at the level of the thyroid capsule to ligate the superior thyroid vessels. The nerve branches into two primary branches:
    a. External branch — this is primarily motor in function, and it innervates the inferior constrictor and cricothyroid muscles. It then divides into branches, which enter the lateral inferior pharyngeal constrictor muscle and the cricothyroid muscle, and the superior pole.
    b. Internal branch — this is sensory to the larynx, and it enters the larynx through the thyrohyoid membrane.
2) Recurrent laryngeal nerve — the recurrent laryngeal nerve (RLN) provides both sensory and motor function to the larynx. This nerve is sensory to the subglottic region and innervates all muscles to the larynx except the cricothyroid muscle. The RLN provides motor function for both vocal cord abduction and adduction.

The RLN is associated with the inferior thyroid artery at approximately the junction of the lower and middle thirds of the thyroid gland. On the left, the RLN ascends in the tracheoesophageal groove and crosses deep to the inferior thyroid artery; on the right, the RLN crosses more obliquely and is oriented more laterally than caudally. The RLN also may bifurcate or trifurcate prior to insertion in the cricothyroid muscle. The motor function for adduction and abduction is located in the anterior branches of the RLN.

Palpation of the tracheoesophageal groove and the junction with the inferior edge of the thyroid cartilage identifies the approximate location of RLN insertion into the trachea. The nerve itself may also be palpated in the tracheoesophageal groove.

Right recurrent laryngeal nerve — the right RLN originates from the right vagus nerve at the level of the subclavian artery. It courses posterior to the subclavian artery, taking a transverse course as it travels superiorly towards the lateral trachea and into the tracheoesophageal groove. It courses through the ligament of Berry and enters the larynx through the first tracheal ring, inferior to the cricothyroid muscle. It is common to see several branches of the right RLN as it approaches the trachea. The most anterior branch of the right RLN is the crucial motor branch.

Left recurrent laryngeal nerve — the left RLN originates from the left vagus nerve at the level of the aortic arch. It courses posterior to the aorta at the ligamentum arteriosum, taking a direct superior course toward the tracheoesophageal groove before entering the larynx in a similar fashion to the right laryngeal nerve. The left RLN thus courses more directly superiorly than the right nerve, and enters the tracheoesophageal groove at a level lower than the right RLN, which takes a more transverse course.

Non-recurrent laryngeal nerves — a non-recurrent RLN may be present in nearly 1 percent of patients. When present, the nerve will course directly from the vagus nerve to the trachea.

Rarely, the right inferior laryngeal nerve may not recur and instead crosses transversely from the vagus nerve and behind the common carotid artery; in almost all instances, it enters the larynx at the usual level. Non-recurrence of the inferior laryngeal nerve results from a vascular anomaly during embryonic development of the aortic arches in which the fourth vascular arch and right dorsal aorta involute, causing the aberrant development of arterial structures on the right,

including the lack of an innominate artery and the passage of the subclavian artery behind the oesophagus.

A non-recurrent left inferior laryngeal nerve would require a right aortic arch associated with situs inversus and is exceedingly rare.

Nerve injury — Nerve injury can result from the disease process, surgery, or airway access for anaesthesia. Injury to the superior laryngeal nerve results in voice weakness or fatigue as well as changes to both voice quality and pitch.

Injury to the recurrent laryngeal nerve (RLN) may result in paresis or paralysis of the true vocal cord to a paramedian or lateral position. Intrinsic muscles of the larynx, aside from the cricothyroid muscle, can be impaired and the patient may have swallowing dysfunction with an aspiration risk. A bilateral injury to the RLN may necessitate a tracheostomy.

Lymphatic drainage -

The neck is divided into compartments based on patterns of lymphatics. The central compartment (level VI) is the primary lymphatic drainage region for the thyroid gland. The central compartment is bounded superiorly by the hyoid bone, laterally by the common carotid arteries, and inferiorly by the innominate artery just caudal to the suprasternal notch.

3.8 Physiology of thyroid gland

How does the thyroid gland affect metabolic activity?

The thyroid gland tissue is composed of follicles. Each follicle functions as an independent storehouse of colloid, which in turn is what acts as the centre of thyroid hormone production. Iodine is the essential component for this.

Synthesis and release of thyroid hormones:

Iodide trapping – TSH binds to its receptors in the follicle cells, which causes transport of iodide ions across the cell membrane and thus causes concentration at a level much higher than the blood.

Oxidation – The ions undergo oxidation in the lumen of the follicular cells. This results in formation of iodine, which is then transported across the membrane into the colloid.

Formation of T3, T4 – The peroxidase enzymes in the colloid link the iodine to the tyrosine amino acids in thyroglobulin. This produces two intermediaries which with covalent binding form either **triiodothyronine** (T_3), or **thyroxine** (T_4)

These newly produced hormones stay in the colloid until TSH mediated endocytosis back into the follicular cells. The thyroglobulin colloid is broken down by lysosomal action into free T3 and T4, which enter the blood stream by diffusion across the membrane.

In the bloodstream, about 99 % of the circulating T3 and T4 are bound to specialized transport proteins, mainly thyroglobulin binding proteins, albumin, or other plasma proteins. This bound form prevents free diffusion into cells. Only less than one per cent remains in unbound form.

Bound hormones are easily released when required from the plasma proteins to facilitate entry into target cells.

Regulation of TSH synthesis:

A classic negative feedback loop controls the regulation and release of thyroid hormones. Thyrotropin releasing hormone, or TRH, is secreted by the thalamus. This acts on the anterior pituitary to release TSH. TSH in turn acts on the thyroid gland to stimulate release of thyroid hormones.

3.9 Functions of thyroid hormones

Now that we have a brief overview of the anatomy and physiology of the thyroid gland, we have the prerequisite knowledge to understand about its functioning.

The thyroid gland is a major hormonal organ. Its hormones play a major role in metabolism, growth and development of the human body. The various important functions are listed below:

1) Growth – the thyroid hormones have significant effect on post-natal growth and bone maturation. There is definitive evidence of growth retardation in children with thyroid hormone deficiency. The complex physiological process of growth is dependent on the growth promoting effect of the thyroid hormones.
2) Development – normal development of the foetal and neonatal brain relies on normal levels of thyroid hormone in the bloodstream.
3) Metabolism – most tissues in the body are stimulated by various ways by the thyroid hormones. This essentially causes increase in the basal metabolic rate. Its specific action on fat is that it causes mobilization, leading to increased concentration in plasma. Also oxidation of fatty acids is stimulated. Thyroid hormone levels and blood cholesterol

concentration is inversely proportional. Carbohydrate metabolism is also influenced by thyroid hormones – increased gluconeogenesis and glycogenolysis occurs as a result.

4) Cardiovascular effects – thyroid hormones increase heart rate, cardiac contractility and cardiac output. They also promote enhanced blood flow to many organs by vasodilatation.

5) Central nervous system effects – this effect is especially important in the context of quality of life. Hypothyroidism leads to sluggishness, lethargy, slowed thinking, and depression. On the other hand, hyperthyroidism leads to anxiety, excessive irritability, insomnia and agitation.

6) Reproductive system effects – normal levels of thyroid hormones are essential for healthy reproductive functioning. Hypothyroidism in particular is associated with infertility.

So how can thyroidectomy affect quality of life? Good surgical handling is important for the same, and is described below.

3.10 Surgical technique of Thyroidectomy

A slightly curved transverse skin crease incision is made approximately 2 cm above the sternum, along the Langer's line of skin. The incision is deepened through the skin, subcutaneous layer and through the platysma muscle. The skin flaps are raised by dissecting them away from the strap muscles. The superior end of dissection is the thyroid cartilage and the inferior extent is the sternal border.

The thyroid capsule is approached by splitting the strap muscles in the midline. By blunt dissection mainly, the anterior aspect of the gland is exposed. The middle thyroid veins should

be isolated and ligated. The lateral aspect of the lobes should be properly exposed with the help of de Quervain retractors. The strap muscles may be divided when necessary.

Lateral retraction of the upper pole is done to open up the avascular space between the lobe and the cricothyroid muscle. This exposes the external branch of the superior laryngeal nerve. The superior vessels are ligated with transfixing sutures (9).

The isthmus is freed from the trachea and divided between transfixing ligatures. The pyramidal lobe, usually arising from the left lobe is traced upward and removed.

The hilar structures can be tackled only after complete division of the superior vessels and medial rotation and anterior mobilization of the lobe.

Thomas et al described capsular dissection, and this involves development of a plane between the capsule and the tertiary branches of the inferior thyroid artery. The branches are ligated individually on the surface of the gland.

This method lowers the possibility of damaging the RLN and the parathyroid glands.

Further careful dissection helps in identification of the RLN and the parathyroid glands.

It is important to preserve as many branches of the inferior thyroid artery as possible, as the blood supply to the ipsilateral parathyroid glands is dependent on these.

Truncal ligation of this artery should be avoided. A vessel loop can be used if necessary to facilitate adequate exposure of the RLN.

The tubercle of Zuckerkandl acts as a good landmark for the RLN. The nerve is found traversing posteriorly to the thyroid gland and below the Berry's ligament. The RLN never enters the ligament though, and is found laterodorsal to the ligament.

The left RLN leaves the vagus nerve and hooks around the aorta, and ascends again similarly to the right RLN laterally to the trachea, to finally give branches to the laryngeal muscles. Identification of the nerve can be aided by palpation. Identification of the crossing point of the RLN and inferior thyroid artery is essential. Gentle dissection with a fine tip curved artery / haemostat is required. Though there are various anatomic variations, this crossing point is a constant anatomic landmark to identify the RLN.

However, the non-recurrent laryngeal nerve is an exception, which is associated with an anomalous right subclavian artery and is almost always found on the right.

All identified parathyroid glands must be preserved, irrespective of the extent of thyroidectomy. The best way to do this is capsular dissection, as they can be swept off the surface of the gland and be retained with intact vascularity. The superior parathyroid is identified after mobilization of the superior pole. The inferior parathyroid is usually found near the inferior pole, or sometimes within the thymus. Devascularized but normal parathyroid should be auto transplanted.

After proper exposure of the RLN, the vessels going to the lower pole are transected. An accessory ima artery may be found entering the lower pole in about 12 % of cases, which may cause intra operative bleeding (9).

The final steps include dissecting the thyroid away from the trachea with a watchful eye on the RLN. The dense attachments at the level of Berry's ligament require sharp dissection with ligation of the superior branch of the inferior thyroid artery (which crosses beneath the nerve into the gland). Thermal dissection devices should be avoided at this step to prevent injury to the RLN.

A drain may be placed after adequate haemostasis. The strap muscles, platysma, and skin are approximated.

3.11 Complications of Thyroidectomy

Post thyroidectomy complications can be transient or permanent. The transient complications vary between being life threatening to being subtle, but the permanent complications remain a major concern for the operating surgeon and the affected patient.

During thyroidectomy, nerves, blood vessels, parathyroids are all at risk of injury during dissection. The important post-operative complications are outlined below:

1) RLN injury:

   As the nerve is a mixed motor, sensory and autonomous nerve, many effects to voice or swallowing or both together can occur.

2) Superior laryngeal nerve injury:

   Injury to this nerve can result in voice fatigue, huskiness, and inability to sing at higher pitches.

3) Cervical sympathetic chain injury:

   This can result in Horner's syndrome, with a higher risk of occurrence in invasive malignancies and retro oesophageal goitres.

4) Hypocalcaemia:

   This could be transient hypocalcaemia, which can occur in almost 50 % of cases, or rarely, permanent.

5) Hematoma:

Hematomas and fresh bleeding would require immediate re-exploration

6) Bilateral vocal cord dysfunction with airway compromise:

This grave condition would necessitate immediate re-intubation and tracheostomy.

7) Seroma:

This would need aspiration to relieve discomfort.

8) The other infrequent complications are wound infection, and injury to major structures like carotid artery, oesophagus, jugular vein.

3.12 Current complication rates

Even though the perioperative mortality rate is very low, the unplanned emergency department visits and readmission rates can be quite frustrating. In a recent study done by Joseph et al, the rate of re-operations, emergency department visits, and hospital readmissions were 3.4%, 0.6% and 3.0 % respectively (10).

Post-operative haemorrhage is the most life threatening and most common cause of unplanned re-operations. The incidence of hematoma in the post thyroidectomy setting ranges between 0.3 to 2.2 % (10). The dramatic course of events following bleeding or hematoma leads to acute respiratory compromise, making this the most feared complication.

In a large, multi institutional risk-adjusted American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, the 30-day morbidity and mortality after total thyroidectomies was calculated using the data of 40,025 patients in the period from 2005 to 2014. The study proved that the rate of complications such as sepsis, septic shock, readmission,

re-operation were all statistically significant. They also found that this risk of complications was higher in patients admitted as in patients in comparison to outpatient operations (11).

In a study done by Miguel Ernandes et al, the rate of transient complications was 18.86%, which included transient hoarseness in 6.57 %,transient vocal cord paralysis in 0.43%, and transient hypocalcaemia in 9.21 %(12).

The permanent complications included hypothyroidism in patients post partial thyroidectomy at 9.65%, and permanent unilateral vocal cord paralysis at 1.75%.

Literature from many other international studies has estimated the risk of and permanent unilateral vocal cord paralysis ranging between 0.2% and 5 %(12).

They had concluded to have considerably high rates of undesirable complications post thyroidectomy, especially in patients with compressive symptoms, shorter history, malignancies and radical surgeries.

In conclusion, surgery remains a mandatory option for thyroid malignancies. But for benign thyroid diseases, surgery is just one of the treatment modalities. Keeping in mind the possible peri-operative complications, treatment should be customized for every patient. Knowing that most benign thyroid diseases are chronic and long standing, is the surgeon putting his best foot forward by offering operative management?

As we have come to realize over the ages the impact of benign thyroid disease on quality of life, improvement versus deterioration in quality of life post thyroidectomy has become a topic of much contemplation and discussion.

3.13 Quality of life

There are myriads of reasons to be interested in looking at benign thyroid diseases and the patient's perception of the impact on quality of life suffering from these.

Firstly, like mentioned earlier, the burden of thyroid disease globally is that of epidemic proportion. There are also a large number of undiagnosed and untreated patients.

Secondly, this spectrum of disease is seen affecting all age groups. Ranging from endemic goitres to toxic nodular goitres, various age groups are affected by this disease in different forms.

Thirdly, the clinical presentation of this disease, especially benign disorders, is very subtle. Many patients don't seem very symptomatic, but on assessment are found to have a poor quality of life attributed to this disease and its branches into important aspects of life.

Quality of life studies have become increasingly important in this generation. Especially for diseases that are chronic and do not take a dramatic turn of events over the years, the effect of living and adapting with the disease tends to have many varied effects that undermine day to day life functioning. The disease subtly runs like a constant undercurrent that streams into social, economic and emotional aspects of daily living without us being able to pin down slow changes to the disease as such.

Quality of life can be thought of as subjective illustration from the patient's perspective. It can be defined exclusively by the patient. It has been defined by the WHO working group as a personal evaluation of position in life based on relation to individual and/or cultural standards, values, expectations and goals (13). The term 'well being' as significantly added into the WHO definition of health has developed into an indispensable component of quality of life assessment.

To encompass this component, at least three dimensions are incorporated into QOL studies – physical, mental and social functioning to provided a wholesome idea of well-being.

Health related Quality of life is the evaluation of the impact of a disease and its treatment on all relevant dimensions of the patient's life. It is a multi dimensional concept that goes beyond direct measures of health. Health related quality of life is usually assessed by administering a self-completed questionnaire integrating many domains, quantifying various aspects of health.

There are two types of HRQOL measures, mainly generic and disease specific. The generic type can be applied to many dissimilar diseases, and thus applicable to a wide spectrum of diseases. Disease specific instruments are designed to measure the impact of a specific disease on patients' QOL.

One such health related quality of life questionnaire, was developed by Torquil Watt from the Department of Endocrinology, Copenhagen University Hospital, Rigshospitalet and Health Service Research, for assessing quality of life in benign thyroid diseases (14)It was originally developed in Danish, and was validated after undergoing four stages of development, namely:-

Phase I: Issue generation - Relevant issues related to thyroid related quality of life were identified

Phase II: Operationalisation - Draft questionnaire was made by conversion of relevant items into items

Phase III: Pretesting - Cognitive interview techniques were used to test and modify the questionnaire

Phase IV: Quantitative scale validation - Testing of constructed scales in a large sample.

This questionnaire is called the ThyPRO – where PRO stands for patient reported outcome, which is a new concept in the world of quality of life studies. During patient and expert interviews, a wide spectrum of aspects relevant to patients like fatigue, cosmetic complaints, eye symptoms, etc were identified. Both directly specific and non-specific aspects of high importance were taken into consideration. The questionnaire developed has 84 items of 13 scales, plus one item that measures overall quality of life.

The Likert scale is used to rate each item on a scale of 0 to 4. Thirteen scales of 0 to 100 are formed by taking the average score of items on each scale divided by 4 and multiplied by 100 (15). Higher scores imply worse health status.

A reference period of 4 weeks in the questionnaire for each item was decided to give adequate time between initiation of treatment and to remove the bias of persisting thyroid hormonal level.

This questionnaire has been validated in multiple languages after being originally developed in Danish. It was found to a comprehensive instrument with a wide range of possible applications. The response acquired with this specific questionnaire was found to be significant in comparison with generic health related questionnaires like Short Form Health Survey-36.

Soon after the development of ThyPRO, the global application across cultures and countries was being contemplated upon. It was thus translated and validated in seven countries – namely, UK, Netherlands, Serbia, Italy, India, Denmark and Sweden. The translations were compared with the English version. It was then declared to be cross culturally valid with only minor cross-cultural invariance, and thus recommended for use in international multicenter studies (14).

The ThyPRO questionnaire now exists as translated and validated versions in German, Dutch, Italian, Swedish, French, Portuguese, Arabic, Simplified Chinese, Traditional Chinese, Tamil, Romanian, Bulgarian, Spanish, Hindi, Serbian, and Polish (16).

The ThyPRO was found to be a very thorough but elaborate and time-consuming questionnaire. A shorter version was required so as to enhance applicability and ease in daily clinical settings. At the same time preservation of the design in terms of construct and measurement properties was debated upon.

This led to the evolution of the ThyPRO 39, an abridged and thus condensed version of the original ThyPRO. The analysis for developing a shorter version was done in three steps:

1) Selection of items
2) Scoring of short scales
3) Validation of this shorter questionnaire (17)

Some scales like the hypothyroid scale were retained as such, whereas 'impaired sex life' was excluded because of lower acceptability. The Item Response Theory (IRT) model was then used to analyze the other items to select the best items.

The number of items on each scale was reduced to an optimal minimum of three. The Orlando and Thissen IRT based summed score linking was used to score the short form scales.

Clinical validity and test – retest reliability were then evaluated for scale validation.

Agreement plots comparing the original version and the abridged version demonstrated uniform agreement across the whole spectrum.

Thus the abbreviated version of the ThyPRO consisting of 39 items was developed, with the following scales:-

1) Four physical symptom scales
2) Seven scales of physical, mental, social well being
3) One scale for appearance
4) One scale for overall quality of life

This version with fewer items and preserved good measurement properties has made best use of various methodologies and integrated them into providing a successful outcome.

The ThyPRO 39 has been used in international studies and also been validated in other languages to enhance widespread applicability.

The process of translation and validation involves the following steps: -

1) First forward translation
2) Second forward translation
3) Reconciled translation
4) Back translation
5) Revision by the in country consultant and developer of ThyPRO
6) Testing of pre final version by cognitive interview techniques
7) Finalization of translation

Wong, Choi, Woo, Lang et al evaluated the validity of ThyPRO 39 for Chinese patients with benign thyroid diseases. They concluded that improvement of eight items would be required to produce a more valid Thy PRO 39 instrument (18).

Similar translation and validation of the ThyPRO 39 was done in Hindi, Tamil, Greek and Bulgarian, all of which have been put to use in clinical practice.

Thus the impact of thyroidectomy on quality of life in benign goitres, which was previously very much unstudied, has now emerged as a matter of great importance. Customized decision to offer operative management will soon be influenced by how positively the quality of life can be changed post operatively. If in multi institutional studies the quality of life is reported as going downhill post operatively, it is possible that non-operative modalities will take precedence over thyroidectomy to offer the best possible quality of life for a patient.

4. Methodology

This study was conducted after obtaining approval from the Institutional Review Board and Ethics committee of the Christian Medical College, Vellore (IRB number 10440).

4.1 Study design

This study was designed to be a prospective longitudinal cohort study.

4.2 Population of interest

Patients with benign goitres planned for thyroidectomy between January 2017 and August 2018 were recruited from the surgical wards of Endocrine surgery.

4.3 Inclusion criteria

- Patients with clinically visible goitre, being planned for surgery
- Primary thyroid surgery under Endocrine surgery
- Age more than 18 years
- Pre-operative FNAC: Bethesda category I, II and III

4.4 Exclusion criteria

- Patients with FNAC proven thyroid malignancy or malignancy on final histopathology.
- Patients undergoing thyroid reoperation and/or completion thyroidectomy
- Patients with a pre-operative recurrent nerve palsy (RLN)

- Patients undergoing neck dissection along with total thyroidectomy

4.5 Informed consent administration

All the recruited patients were given an information sheet with details about the study which was also explained to them in their local language. Informed consent was obtained by the principal investigator from the patient after being given adequate opportunity to read the information sheet and ask questions. Consent forms were made available in English, Hindi, Tamil and Bengali.

4.6 Methodology of data collection

Data was collected solely by the principal investigator. The sequence of data collection is detailed below:

1. Patients who were planned to undergo thyroidectomy for goitres were identified preoperatively.
2. Those patients who satisfied the inclusion criteria for the study were recruited after obtaining informed consent. They were given the following documents:
    a. Patient information sheet
    b. Informed consent form
    c. Proforma which obtained the following data: Age, sex, type of goitre, thyroid dysfunction, surgical procedure, duration of symptoms, post-operative hypocalcaemia, specimen weight, specimen dimension and pathology.
    d. ThyPRO 39 questionnaire
3. To assess the current quality of life the ThyPRO 39 questionnaire was administered on the

day prior to the surgery and was filled by the patient with or without the help of the primary investigator or a family member.

4. Patients with final histopathology reports confirming benign disease were marked for the post operative follow up.
5. These patients were reviewed six months after surgery to assess the quality of life post thyroidectomy. The questionnaire was administered either during OPD review, by mail or through a telephonic interview.

4.7 Sample size calculation

The sample size was calculated based on a similar study done in Sanjay Gandhi Postgraduate Institute (SGPGI), Lucknow, India by Mishra et al (19) . The sample size was calculated to detect a 25 or more unit change in Quality of life scores after the surgical procedures. Assuming a within subject standard deviation of 20, an average change of 25 or more with a 5 % level of significance and 80% power, we estimated sample size of 25 for results to be statistically significant.

Knowing our institutional rate of malignancy on the final histopathology report to be around 60%, we recruited 100 patients who fulfilled the inclusion criteria and downsized the sample size after obtaining the post operative histopathology reports.

Formula

$$n = \frac{z^2_{1-\alpha/2}\sigma^2}{d^2}$$

Where,

σ : Standard deviation

d : Precision

1- α/2 : Desired Confidence level

Standard Deviation	**20**
Power	**80%**
Significance value	**5%**
Required sample size	**25**

4.8 Data collection

The data was initially entered on a patient proforma sheet. The detailed clinical data was then obtained from the computerised hospital information system. The complete data was finally entered using EpiData Manager and EpiData Entry Client (v 3.1).

4.9 Data analysis

Baseline study variables were summarised using descriptive statistical methods. The distribution of QoL was assessed and if found to follow normal distribution, a paired-t-test was used to

compare the average QoL in pre and post-surgical procedure. Alternative non-parametric tests were used when the distribution was skewed. To identify factors related with post-operative QoL, regression methods were used.

4.10 Research instrument

The ThyPRO questionnaire consists of 12 domains consisting of 85 items. As the questionnaire was found to be rather lengthy and thus time consuming, a shorter abridged questionnaire called the ThyPRO 39 was created by the same author, Torquil Watt (17). This has 39 items for evaluation of quality of life. It was found to have very high agreement with the original long-form ones, with good test–retest reliability (14). The mean duration for competing this was also remarkably shorter. The abridged validated version of the ThyPRO questionnaire was the research tool used for analysis. This tool analysed quality of life with twelve main domains and sub set questions, totally a number of 39 points for analysis. The same questionnaire was administered post operatively.

The proforma given to the patients had these following demographic variables, along with variables that were included to assess quality of life:

a) Age
b) Gender
c) Duration of symptoms
d) Duration of hormonal dysfunction
e) Functional status
f) Type of goitre
g) Retrosternal extension
h) Type of surgery

i) Preoperative FNAC

j) Final histopathology

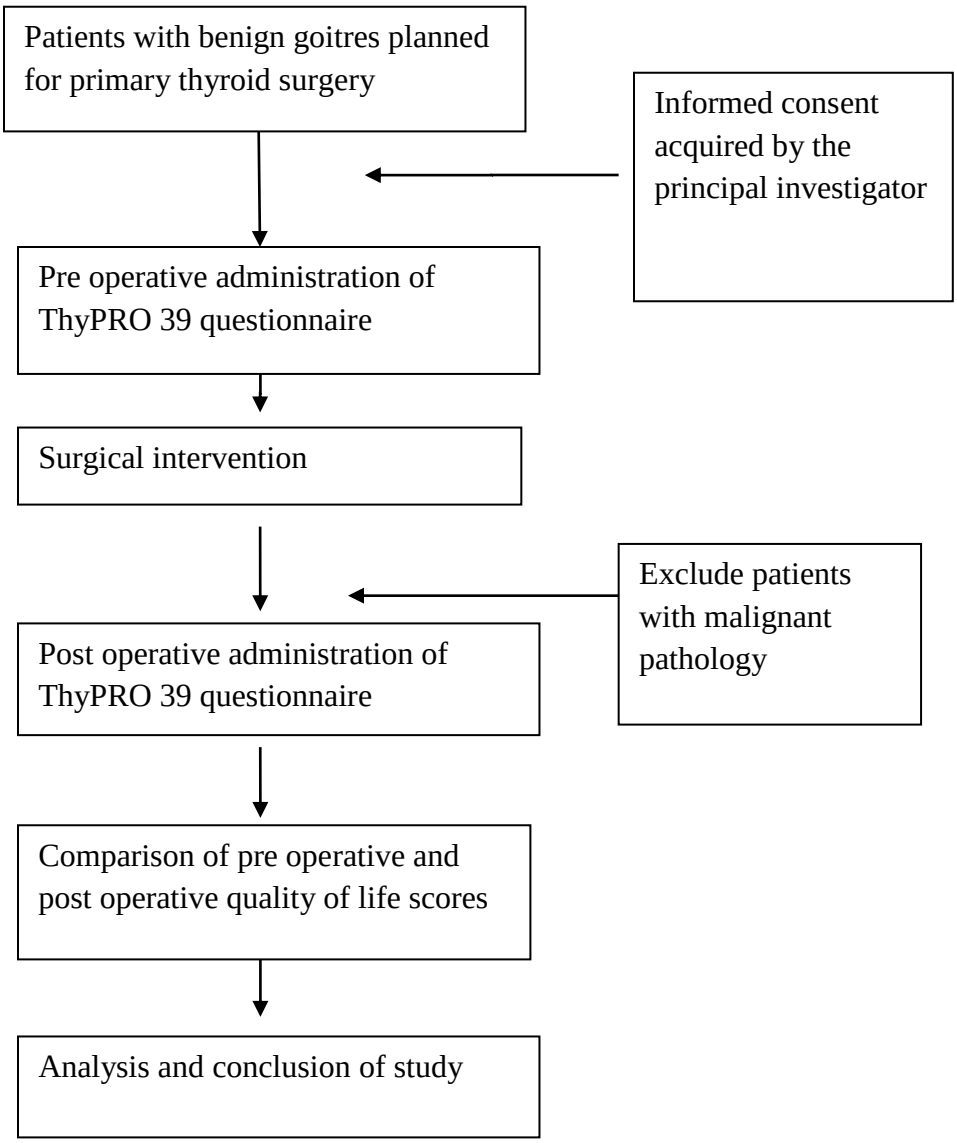
k) Gland weight

l) Dimensions of goitre

m) Post operative hypocalcaemia: Defined as next day postoperative PTH <8pg/ml.

n) Post operative recurrent laryngeal nerve (RLN) palsy: Patients with post-thyroidectomy voice change underwent a NPL scopy. Documented vocal cord palsy on postoperative NPL was recorded as RLN palsy.

5. Study algorithm



6. Results

Hundred patients with thyroid nodules whose FNAC report was benign or indeterminate and undergoing surgery, were initially recruited for this study between January 2017 and August 2018. Histopathology revealed malignancy in 45 and hence they were excluded. Follow up data was unavailable for another five patients and they were also excluded. The remaining 50 patients with benign histopathology were finally included in the study.

6.1 Analysis of proforma variables

Age

Among the 50 patients, the minimum age was 19 years and the maximum was 67 years. The mean age was 43.30 years with a standard deviation of 11.61.

Gender distribution

A female preponderance was noted in the study cohort (34:16) (figure 6.1.1).

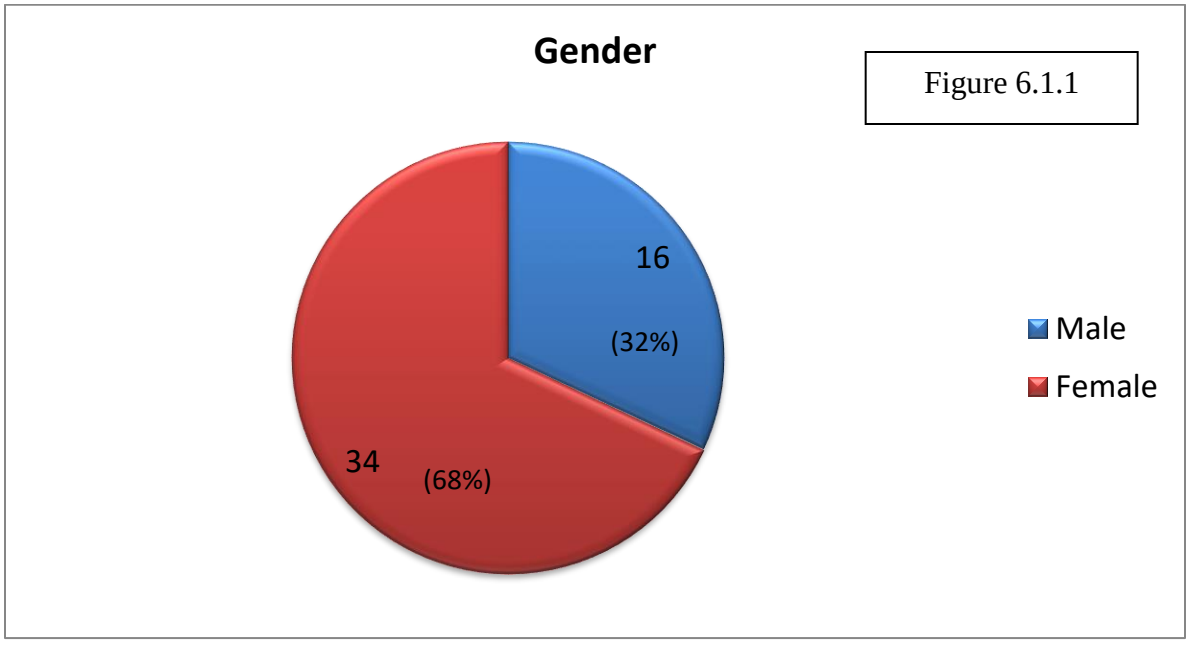


Figure 6.1.1

Duration of symptoms

The duration of symptoms ranged between 1 month to 180 months with a mean of 49.46 months and standard deviation of 40.40 months. Being a skewed variable, the 25th percentile was observed to be 24 months and the 75th percentile was 60 months, with the median being 36 months.

Functional status

Majority of patients were euthyroid 37 (74%), while 12 (24%) were hyperthyroid and only one (2%) was hypothyroid (figure 6.1.2).

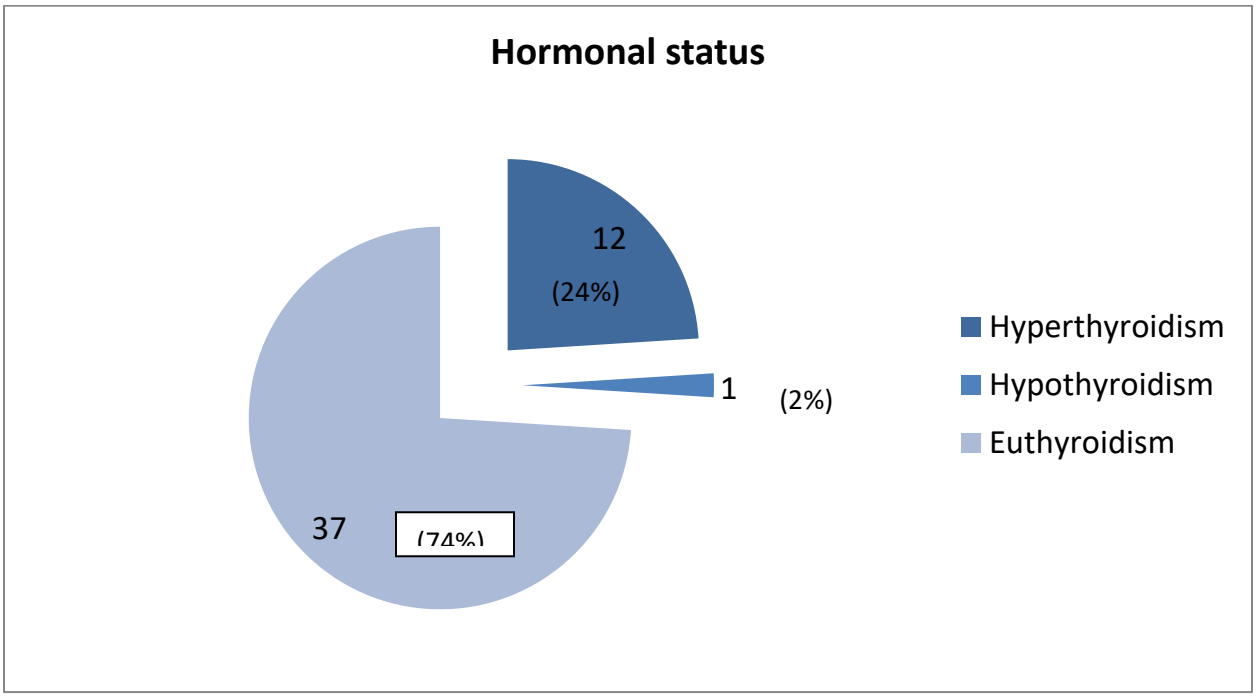


Figure 6.1.2

Duration of hormonal dysfunction

Among the patients who had either hypothyroidism or hyperthyroidism, the range of hormonal dysfunction varied between 5 to 120 months. The mean was 39.92 months and standard deviation was 28.35 months. As this was a skewed variable, the 25th percentile was observed to be 24 months and the 75th percentile was 48 months, with the median being 36 months.

Type of goitre

The most common presentation was a multinodular goitre in 23 (46%) followed by a solitary nodule in 15(30%) (figure 6.1.3)

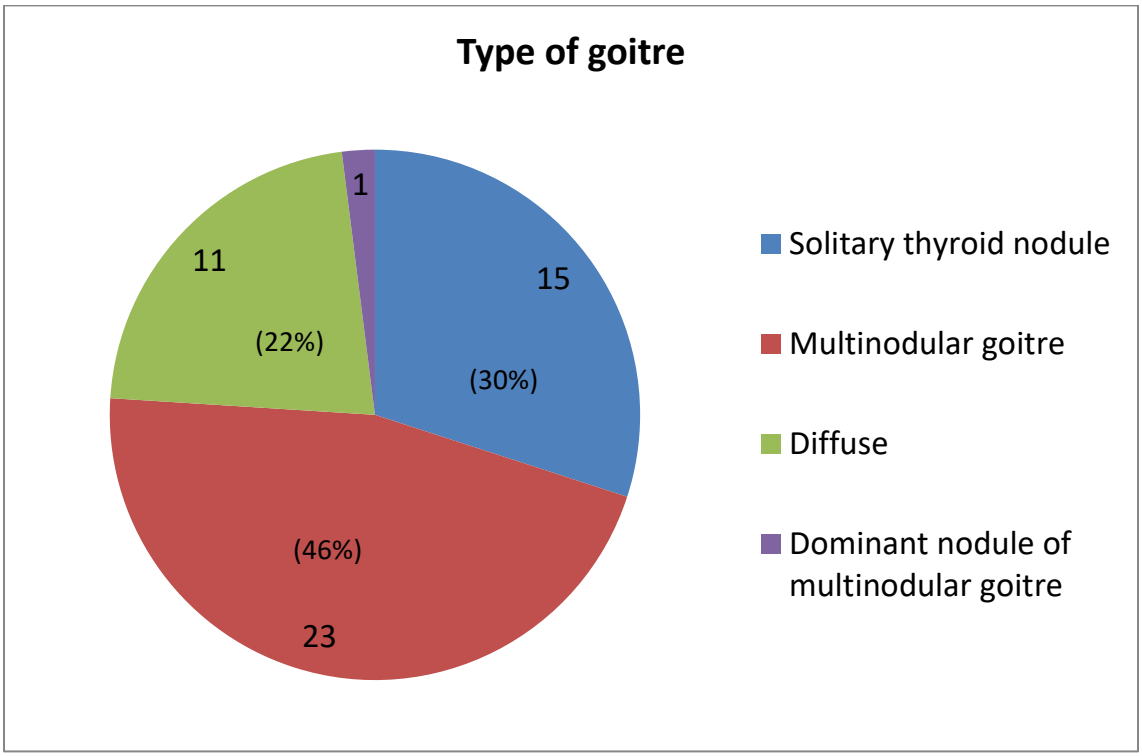


Figure 6.1.3

Retrosternal goitre

There were no patients with retrosternal extension of the goitre in this study.

Indication of surgery

The most common indication for surgery was progressive increase in size of the goitre (62%) while hyperthyroidism (24%), voice change (8%) and dysphagia (6%) accounted for the remaining patients (figure 6.1.4).

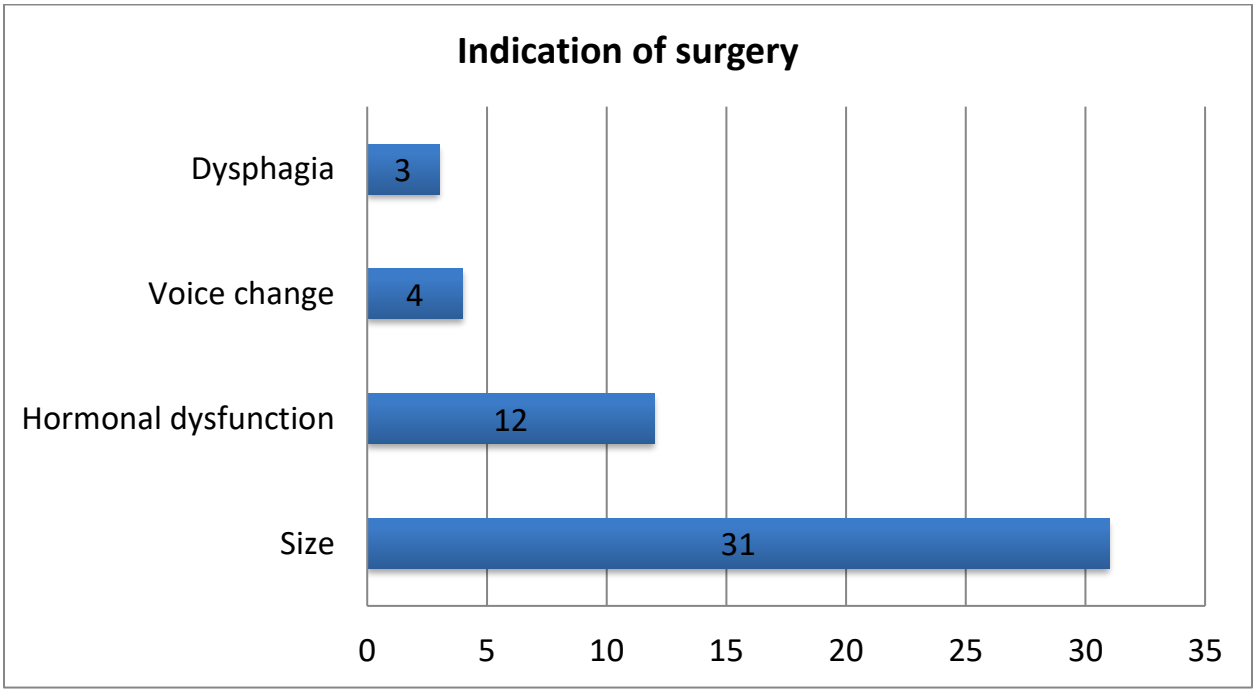


Figure 6.1.4

Operation performed

Forty-five patients (90%) underwent total thyroidectomy while the remaining five (10%) underwent a hemithyroidectomy (figure 6.1.5). Three out of these five patients underwent trans oral hemithyroidectomy.

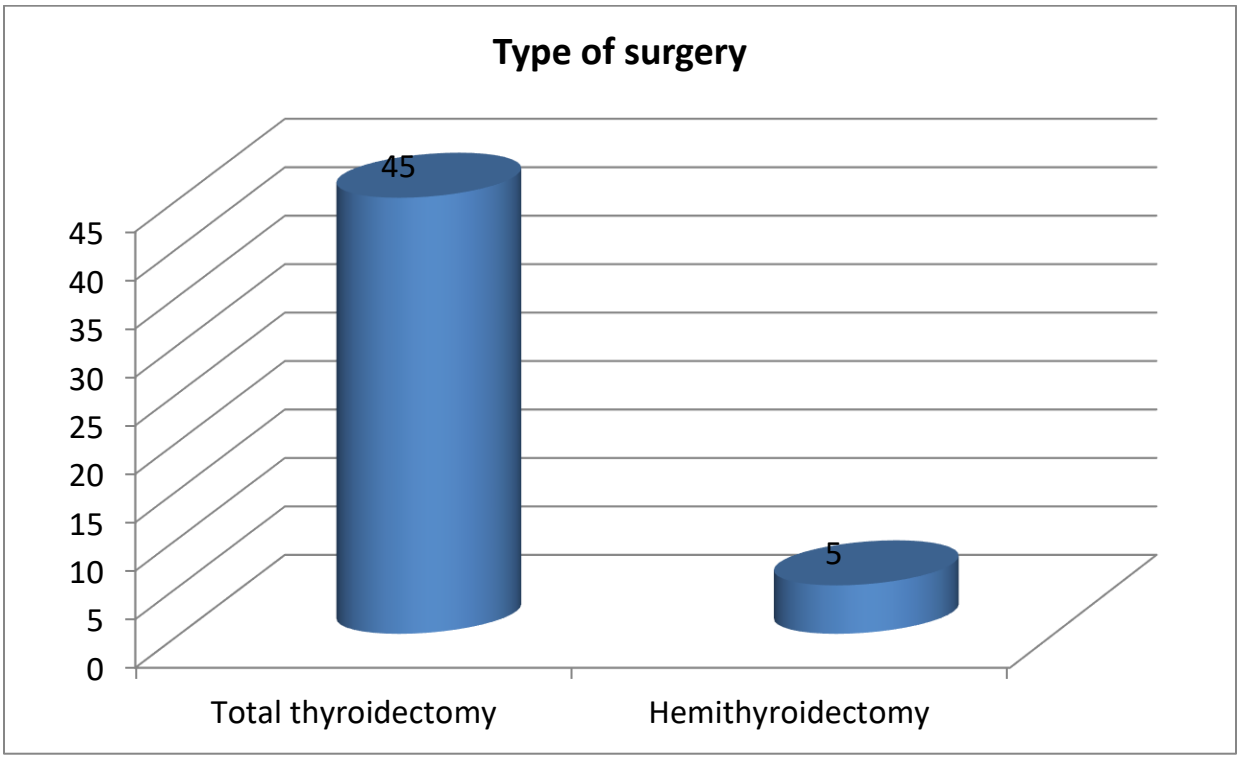


Figure 6.1.5

Dimension

The maximum tumour dimension in centimetres on the histopathology report was documented. The minimum dimension was 0.7cm, and the maximum was 11 cm. To simplify the analysis, an arbitrary size of 5 cm was chosen (figure 6.1.6).

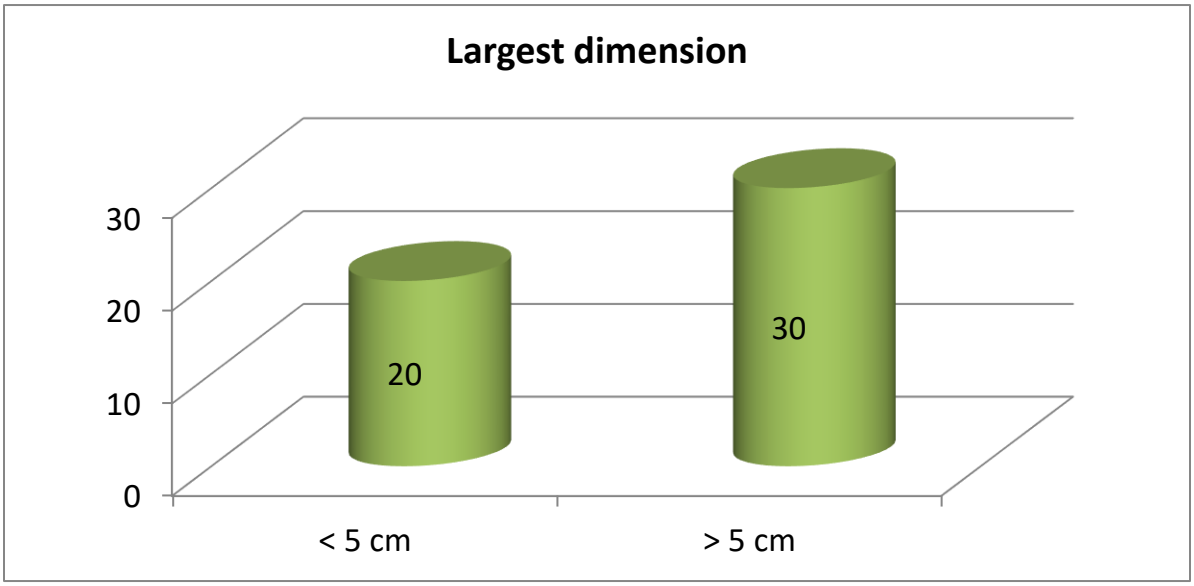


Figure 6.1.6

Gland Weight

The weight of the thyroid gland ranged between 10 gm to 500 gm, with the mean weight being 73.62 gm and standard deviation of 82.97.

Final histopathology

The final histopathological reports were classified into nodular/adenomatous hyperplasia, thyroiditis, Graves' disease and adenoma. There were 7 patients with microcarcinomas and in all seven of them histopathology showed a background of nodular hyperplasia. Patients with micro carcinomas were included in the study as they were managed as benign goitres. All seven patients have been added to the 24 patients with only nodular hyperplasia on histopathology resulting in a total number of 31. This was the largest group in this cohort (figure 6.1.7)

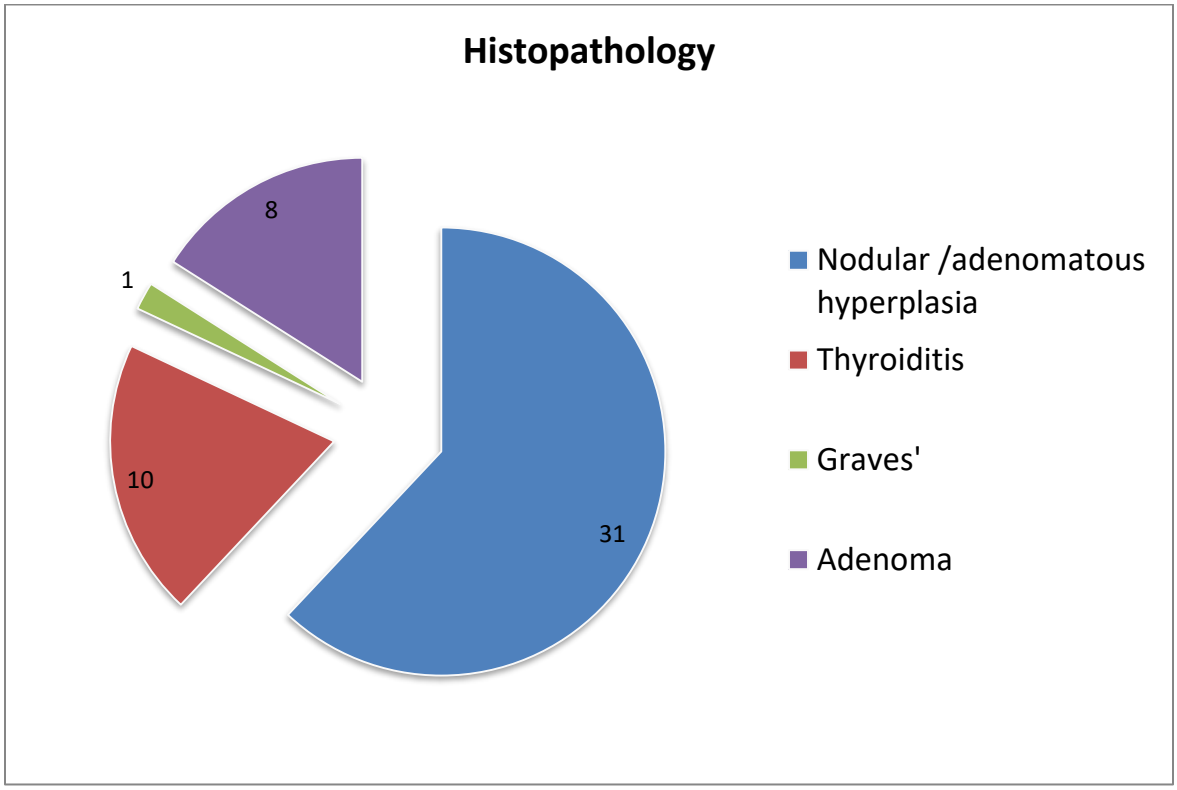


Figure 6.1.7

Post-operative complications:

1. **Post-operative hypocalcaemia**

Fifteen patients (30%) developed immediate post-thyroidectomy biochemical hypocalcaemia. Among them 3 were symptomatic. All fifteen patients received calcium and active vitamin D supplements postoperatively.

PTH was repeated at six months following surgery for 6 patients while the rest only had serum calcium values checked. None of the patients persisted to have biochemical hypocalcaemia or required calcium supplements six months following surgery (figure 6.1.8)

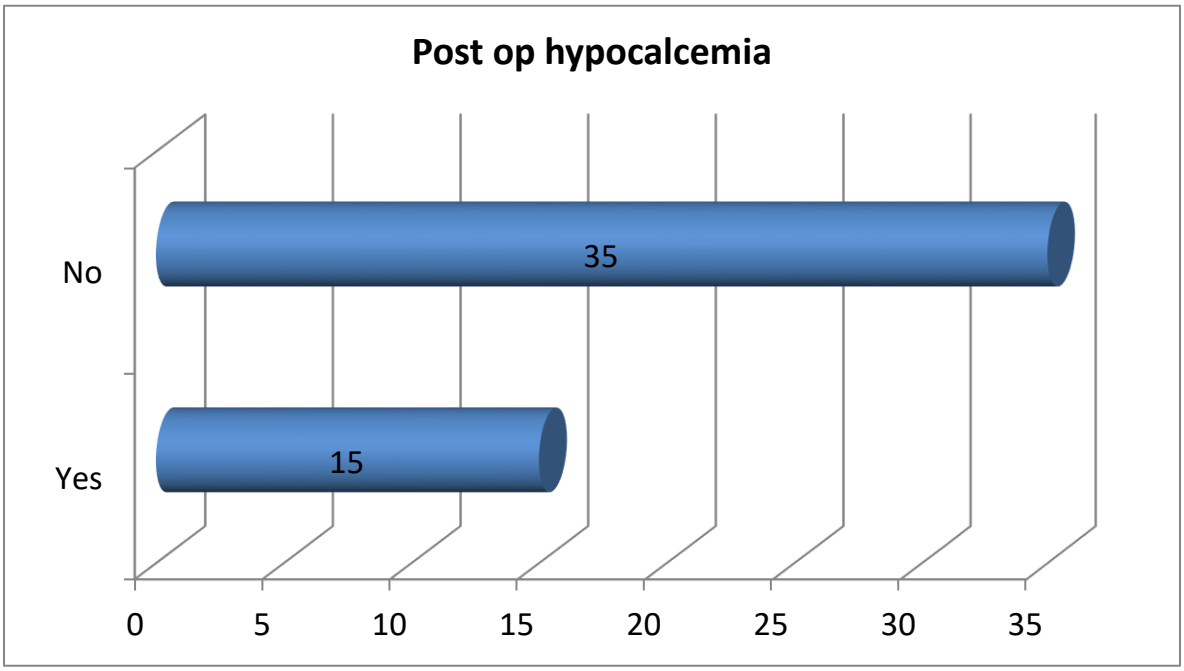


Figure 6.1.8

2. Post-operative RLN palsy

Four patients had a voice change following total thyroidectomy. Nasopharyngolaryngoscopy (NPL) scopy revealed unilateral vocal cord palsy in these four patients. Two of these patients have had a repeat ENT evaluation and NPL scopy six months after surgery, which revealed persistent paralysis. The remaining two are due for a review (figure 6.1.9). To calculate the rate of RLN palsy, nerves at risk (NAR) were estimated. This included two nerves at risk for every total thyroidectomy, and one nerve for every hemithyroidectomy. Therefore, the rate of permanent RLN palsy in this study was 2.1% (2/95). The rate of temporary RLN palsy was also 2.1% (2/95).

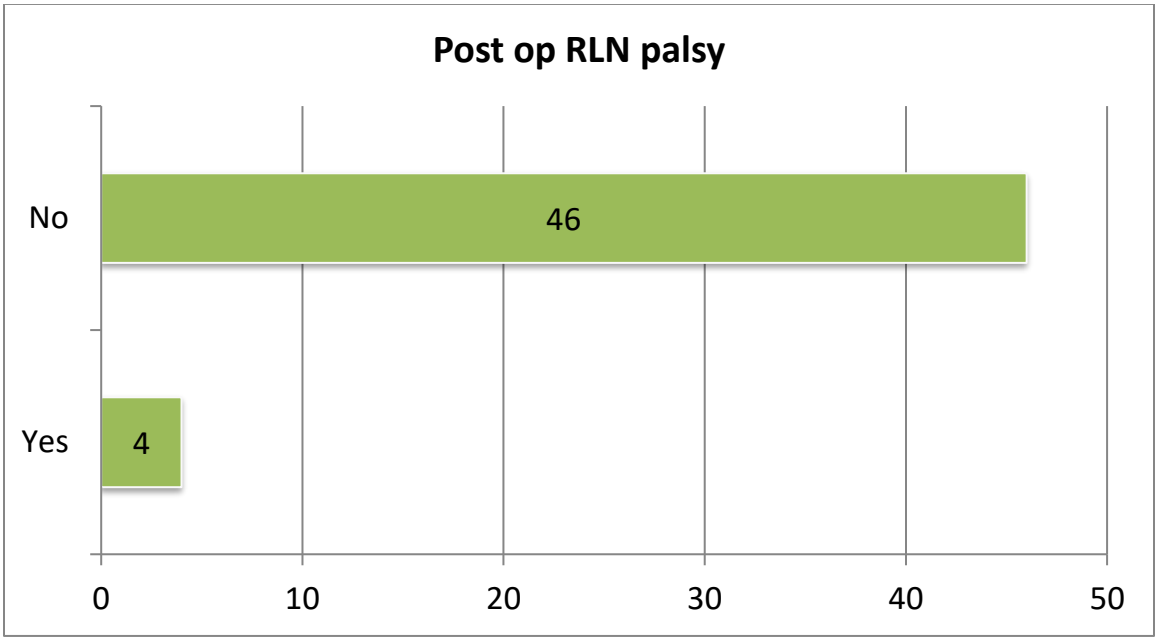


Figure 6.1.9

6.2 Univariate analysis (based on the ThyPRO 39 questionnaire):

All the 12 domains listed in the ThyPRO 39 questionnaire have been considered individually to understand the impact of thyroidectomy on each domain. Each domain evaluated preoperatively was compared postoperatively. As evidenced from the table below (table 6.2.1) there was a significant change in all domains postoperatively except for depression (p=0.126).

Comparison of QOL scores

VARIABLE	PRE OP SCORE	POST OP SCORE	P - VALUE
Goitre	15 (2,26)	2 (2,2)	<0.001
Hypothyroidism	0 (0,12.50)	0 (0,0)	<0.001
Hyperthyroidism	8 (2,18)	2 (2,2)	<0.001
Eye symptoms	1 (1,8)	1 (1,1)	<0.001
Tiredness	42 (33,50)	33 (33,42)	0.003
Cognitive	1 (1,14)	1 (1,1)	<0.001
Anxiety	18 (1,34)	1 (1,10)	<0.001
Depression	29 (29,45)	29 (29,37)	0.126
Emotional	44 (36,52)	36 (28,44)	<0.001
Social life	0 (0,8)	0 (0,0)	<0.001
Daily life	0 (0,15)	0 (0,0)	<0.001
Cosmetic	21 (12,43)	1 (1,1)	<0.001

Table 6.2.1

The composite score preoperative and postoperative were calculated and compared (table 6.2.2). A significant improvement ($p<0.001$) in the postoperative composite score compared to the preoperative score was demonstrated indicating an improved quality of life following surgery.

Pre composite score	Post composite score	P - value
26.91 +/- 11.24	17.75+/- 5.75	<0.001

Difference	Confidence interval
9.16	6.62, 11.70

Table 6.2.2

The above findings have been depicted in the graph below (figure 6.2.1).

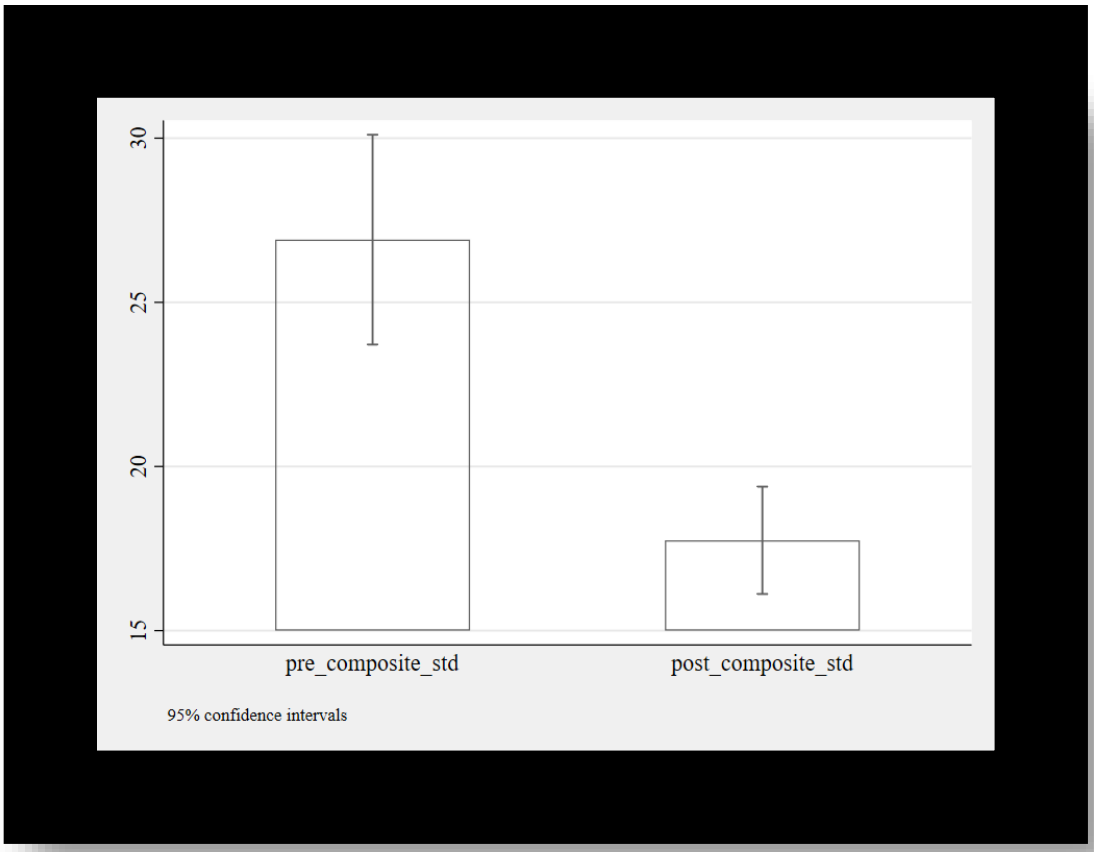


Figure 6.2.1

6.3 Univariate and Multivariate analysis

Factors that could have affected the change in quality of life following thyroidectomy include

1) Age
2) Gender
3) Functional status
4) Hypocalcaemia
5) Type of goitre
6) Duration of symptoms
7) Weight of the gland

These variables have been compared with each individual domain of the ThyPRO 39 questionnaire, the results of which are given in the tables below. A bivariate regression analysis has been done for this study. The results have been tabulated against ten important domains, with exclusion of two domains – impaired daily life (in which the numbers were too low to be tabulated), and overall change in quality of life (which has been calculated separately in the previous section).

1) Age

The comparison between the age groups of more than 40 years and less than 40 years were compared with all the domains, as shown in table 6.3.1. The age group of less than 40 years experienced more symptoms of tiredness and emotional symptoms (p-values of 0.030 and 0.029 respectively)

Age	Age < 40 years	Age > 40 years	P - Value
Goitre symptoms	2 (2, 15)	2 (2, 20)	0.8032
Hypothyroidism	0 (0, 18.75)	0 (0, 25)	0.4475
Hyperthyroidism	2 (2, 33)	2 (2, 13)	0.1702
Eye	1 (1, 8)	1 (1, 14)	0.6941
Tiredness	42 (0, 75)	33 (25, 50)	**0.0309**
Cognitive	1 (1, 21)	1 (1, 14)	0.1285
Anxiety	1 (1, 63)	1 (1, 34)	0.1137
Depression	29 (29, 45)	29 (22, 45)	0.3091
Emotional	36 (28, 68)	28 (21, 60)	**0.0299**
Cosmetic	1 (1, 73)	1 (1, 21)	0.7396

Table 6.3.1

2) Gender

Tiredness, depression and anxiety were significant in females (p = 0.029, 0.037, and 0.007 respectively).

Gender	Male	Female	P-value
Goitre symptoms	2 (2, 15)	2 (2, 20)	0.4657
Hypothyroidism	0 (0, 0)	0 (0, 25)	0.2253
Hyperthyroidism	2 (2, 8)	2 (2, 33)	0.0841
Eye	1 (1, 8)	1 (1, 14)	0.3388
Tiredness	33 (0, 58)	42 (25, 75)	**0.0297**
Cognitive	1 (1, 14)	1 (1, 21)	0.9504
Anxiety	1 (1, 10)	1 (1, 63)	**0.0374**
Depression	29 (29, 29)	29 (22, 45)	**0.0074**
Emotional	28 (28, 60)	36 (21, 68)	0.1183
Cosmetic	1 (1, 1)	1 (1, 73)	0.2253

Table 6.3.2

3) Hyperthyroid status

The presence of hyperthyroidism did not affect any particular domain significantly.

Hyperthyroidism	Absent	Present	P-value
Goitre symptoms	2 (2, 15)	2 (2, 20)	0.9039
Hypothyroidism	0 (0, 18.75)	0 (0, 25)	0.6589
Hyperthyroidism	2 (2, 23)	2 (2, 33)	0.5258
Eye	1 (1, 14)	1 (1, 14)	0.3115
Tiredness	33 (0, 58)	42 (25, 75)	0.2187
Cognitive	1 (1, 21)	1 (1, 7)	0.5751
Anxiety	1 (1, 49)	5.5 (1, 63)	0.1406
Depression	29 (22, 45)	33 (29, 45)	0.0632
Emotional	36 (21, 60)	36 (28, 68)	0.8194
Cosmetic	1 (1, 21)	1 (1, 73)	0.6589

Table 6.3.3

4) Hypocalcaemia

None of the domains were affected by post-thyroidectomy hypocalcaemia, though the domain of emotion reached near significance (p=0.057)

Hypocalcaemia	Absent	Present	P-value
Goitre symptoms	2 (2, 10)	2 (2, 20)	0.7699
Hypothyroidism	0 (0, 0)	0 (0, 25)	0.2472
Hyperthyroidism	2 (2, 33)	2 (2, 23)	0.1081
Eye	1 (1, 8)	1 (1, 14)	0.9273
Tiredness	33 (25, 58)	33 (0, 75)	0.4772
Cognitive	1 (1, 21)	1 (1, 21)	0.6236
Anxiety	1 (1, 26)	1 (1, 63)	0.2954
Depression	29 (29, 45)	29 (22, 45)	0.4469
Emotional	28 (28, 44)	36 (21, 68)	0.057
Cosmetic	1 (1, 12)	1 (1, 73)	0.9385

Table 6.3.4

5) Type of goitre

The type of goitre did not affect any of the domains.

	STN	MNG	Diffuse	P-Value
Goitre symptoms	2 (2, 10)	2 (2, 15)	2 (2, 20)	0.9887
Hypothyroidism	0 (0, 18.75)	0 (0, 0)	0 (0, 25)	0.7737
Hyperthyroidism	2 (2, 23)	2 (2, 18)	2 (2, 33)	0.8292
Eye	1 (1, 8)	1 (1, 14)	1 (1, 14)	0.3421
Tiredness	33 (25, 58)	33 (0, 58)	42 (33, 75)	0.0601
Cognitive	1 (1, 21)	1 (1, 14)	1 (1, 7)	0.7912
Anxiety	1 (1, 49)	1 (1, 34)	10 (1, 63)	0.2449
Depression	29 (29, 45)	29 (22, 45)	37 (29, 45)	0.1981
Emotional	36 (28, 44)	28 (21, 60)	36 (28, 68)	0.1656
Cosmetic	1 (1, 1)	1 (1, 21)	1 (1, 73)	0.8911

Table 6.3.5

6) Duration of symptoms

The duration of symptoms significantly affected the anxiety, emotion and cosmetic domains (p= 0.003, 0.014 and 0.03 respectively).

Duration of symptoms	**r - value**	**P -value**
Goitre symptoms	0.1082	0.4547
Hypothyroidism	0.1507	0.2963
Hyperthyroidism	0.0878	0.5444
Eye	0.0378	0.7946
Tiredness	0.1767	0.2197
Cognitive	-0.1194	0.4089
Anxiety	0.4067	**0.0034**
Depression	0.2487	0.0816
Emotional	0.3453	**0.014**
Cosmetic	0.3017	**0.0333**

Table 6.3.6

7) Weight of gland

The weight of the thyroidectomy specimen did not have a bearing on any of the domains.

Weight of gland	r - value	P -value
Goitre symptoms	-0.1851	0.1982
Hypothyroidism	-0.2515	0.0781
Hyperthyroidism	0.1706	0.2361
Eye	-0.2019	0.1597
Tiredness	-0.1086	0.4526
Cognitive	-0.0696	0.6312
Anxiety	0.1153	0.4251
Depression	-0.1017	0.4822
Emotional	-0.1781	0.2159
Cosmetic	0.0036	0.9801

Table 6.3.7

Univariate analysis of these factors showed a significant association between age (p=0.011), gender (p=0.015) and duration of symptom (p=0.049) with post thyroidectomy improvement in quality of life. The type of goitre on the other hand approached near significance (p=0.053). However, on multivariate analysis none of these factors were significant. The composite score

was the only variable that remained significant on multivariate analysis (0.00). These findings have been depicted in the table below (table 6.3.8).

VARIABLE	UNIVARIATE β , 95 % CI	P - VALUE	MULTIVARIATE β, 95% CI	P - VALUE
Age > 40 years	-4.09 (-7.20, -.98)	0.011	-1.09 (-4.06, 1.88)	0.462
Female	4.16 (.83, 7.49)	0.015	1.60 (-1.50,4.72)	0.303
Hyperthyroid	2.56 (-1.23, 6.35)	0.181	.01 (-5.65 ,5.67)	0.998
Hypocalcaemia	-2.08 (-5.64, 1.46)	0.243	-1.76 (-4.69 ,1.17)	0.231
Multi nodular goitre	-2.77 (-6.42, .87)	0.133	-1.46 (-4.70, 1.75)	0.363
Diffuse	2.02 (-2.38, 6.43)	0.360	-.05(-6.09, 5.98)	0.985
Duration	.03 (.00, .07)	0.049	.02 (-.01, .05)	0.191
Weight	-.00 (-.02, .01)	0.423	-.00 (-.02, .01)	0.554
Pre composite score	.31 (.19, .43)	0.000	.25 (.12, .38)	0.000

Table 6.3.8

7. Discussion

Considering the global disease burden constituted by the spectrum of thyroid diseases, the impact caused by benign thyroid diseases is of great interest and speculation. Over the years many studies had focused their research on thyroid malignancies and their implications in context to quality of life. However, a large proportion of patients with thyroid disorders have subtle benign conditions, and this population was the focus of this study.

Quality of life studies have sparked a great amount of interest over the recent decades. Patient care is evolving from treating simple objective parameters to offering wholesome care with special emphasis on seeking to improve quality of life in emotional, social and functional aspects. Patients with benign thyroid disease may suffer from chronic subtle qualitative issues rather than overtly dramatic objective problems. Hence, improving patient care should include management of factors affecting the quality of life.

The aim of this study was to assess quality of life in patients with benign goitres seeking care at a tertiary hospital and referral centre in south India.

The baseline quality of life was assessed using the well-known and highly recommended ThyPRO 39 questionnaire developed by Torquil Watt, Copenhagen, which was the abridged, cross culturally relevant and shorter version of the original ThyPRO questionnaire developed by the same author. This score was compared with the post operative score measured using the same questionnaire six months from the date of the operation.

The purpose was to establish the baseline impaired quality of life that many of the patients with benign goitres present with in the outpatient department. The ThyPRO 39 questionnaire brings to

light many subtle qualitative issues such as feeling conscious of changes in appearance and being bothered by people looking at them, or causing them to feel a need to change the way they dress. It also highlights problems like difficulty in feeling energetic, or feeling afraid or tense, or not feeling in control of their lives. Finding themselves burdensome to other people and falling into frequent conflicts were also addressed by the ThyPRO 39 questionnaire. Administering the questionnaire made patients consciously aware of how thyroid disease had implications in many essential dimensions of life, which previously were felt subconsciously, much like an undercurrent in their daily lives.

As surgeons dealing with these benign thyroid disorders, there was a pressing need to establish and reflect on whether operative management did indeed improve quality of life significantly in patients, when other modalities of conservative management were available and acknowledged.

A large majority of patients were also afraid of operative intervention – they were wary about the process of undergoing surgery, and the possible post operative complications, some of which were life changing like hoarseness of voice or voice fatigue. To this population, could we reassure them of a definite post operative improvement in quality of life? The ThyPRO 39 questionnaire was found to be a revolutionary tool in this aspect, as it could highlight important subtle qualitative issues pre operatively itself, which could be measured against post operatively – an objective confirmation of subjective improvement.

Hundred patients with thyroid nodules who had a benign or indeterminate FNAC report, were initially recruited for this study between January 2017 and August 2018. Histopathology revealed malignancy in 45 and hence they were excluded. Complete data was unavailable for another five patients, hence they were excluded. The remaining 50 patients with benign

histopathology were finally included in the study. A high rate of malignant goitres is expected being a tertiary referral centre, as majority of patients have been referred for management of possible thyroid malignancy. Further, the yearly annual unpublished audit data in the department where the study was conducted confirms thyroid malignancy rate of 63.52 %.

The age ranged between 19 to 67 years, with mean age being 43.30 years, similar to published Indian literature report by Mishra et al of mean age being approximately 40 years(1). Another recent Indian study on non toxic goitres by Thakkar et al showed a mean age of approximately 33.3 years (20). A large European study is suggestive of a higher middle aged population being commonly affected in high income countries, with a mean age of 56 years(21).

Female gender predominance was observed, with ratio of males to females being 1: 2.12. This was similar to worldwide observation of female predominance, as evidenced by the European study and older studies like the Whickham and Framingham studies (21). A large scale epidemiological study conducted in Chinese women to identify risk factors for goitres and thyroid nodules found various gender related contributory factors like menopause, waist circumference, BMI, hypertension, dyslipidemia and hyperglycaemia(22).

A meta-analysis by Bartsch et al reported that the most common indications for operative management of any goitre included suspicion of malignancy and local compressive symptoms(23). Among benign goitres, Mishra et al found that the most common indication for surgery was thyrotoxicosis (1). Interestingly in the present study we report progressive increase in size of the goitre to be the most concerning indication for the patient to seek operative intervention (62%).

Our department protocol is to perform bilateral thyroid surgery (total thyroidectomy) for patients with bilateral thyroid disease reported on the thyroid ultrasound. In this study 35 patients (70%) had bilateral thyroid disease. Patients with a solitary thyroid nodule, which appears benign on ultrasound and cytology, are counselled regarding diagnostic hemithyroidectomy and the need for a completion surgery in case the final histopathology report is malignant. In India, most patients are not covered by insurance, nor does the government cover the cost of treatment. Considering the costs incurred, majority with solitary thyroid nodule opt for total thyroidectomy upfront after counselling. These factors reflect on the finding that 90% of patients in this study underwent total thyroidectomy while only 10% underwent hemithyroidectomy. Out of 15 patients who had solitary thyroid nodules, 10 of them underwent total thyroidectomy (66.66%).

The mean weight of the gland in this study was reported to be approximately 73 gm. In the study done by Mishra et al, hemithyroidectomy specimen weight was approximately 83 gm, and total thyroidectomy specimen weight was approximately 126 gm (1). The mean specimen weight in an international study conducted in Greece was 40 gm for total thyroidectomy, which also showed that with increase in weight to more than 100 gm, or goitres with intrathoracic component, the risk of post operative hypoparathyroidism was more (24).

The predominant diagnosis based on histopathology reports was nodular or adenomatous hyperplasia, followed by thyroiditis. Patients with micro carcinoma were also included as the management remained the same. Another recently published Indian study had reported colloid goitre followed by multinodular goitre to be the commonest diagnosis based on histopathology(20). A retrospective study done in a tertiary hospital in Nigeria had also showed

colloid goitre to be the most common diagnosis (25). In well developed countries, nodular hyperplasia followed by follicular adenoma were the main post operative histopathology reports (21).

The most common complication following bilateral thyroid surgery is hypocalcaemia. Reported rates of post-thyroidectomy hypocalcaemia worldwide vary between 20-40% in literature. A large retrospective study based on thyroidectomies done by a single high volume surgeon in the United States had reported mild hypocalcaemia to be 22.4% and significant hypocalcaemia to be 29.9% (26).Based on PubMed literature and review of 19 articles, the rate of permanent hypocalcaemia has been reported to be 0-3.5%(27).

An Indian study reported temporary and permanent hypocalcaemia to be 23.6% and 1.61% respectively (28). In this study we report an acceptable rate of 30 % temporary hypocalcaemia, and no permanent hypocalcaemia in comparison.

The reported rates of temporary and permanent RLN palsy in literature vary between 3-8% and 0.3-3% respectively(29). Compared to this an acceptable rate of 2.1% temporary (the two patients awaiting review have been considered temporary palsy) and 2.1% permanent palsy was witnessed in this study. The yearly unpublished data at our centre has recorded RLN palsy between 2.1% and 2.3% over the last five years. As the numbers were small, postoperative RLN palsy was not assessed among the causes for change in quality of life.

The ThyPRO 39 questionnaire is a modification of the ThyPRO questionnaire developed by Torquil Watt to assess quality of life in benign goitres. Patient reported outcome (PRO) has gained increasing precedence and importance especially in terms of chronic diseases. By using the well framed and comprehensive ThyPRO 39 questionnaire for our study population, we

wanted to define quality of life as perceived by the patient alone, and the change and impact felt post operatively.

The ThyPRO 39 questionnaire encompasses twelve important domains. There was a significant improvement in the post operative score in all the domains except depression.

The most affected domain pre operatively was emotional symptoms followed by tiredness. Emotional symptoms were assessed by asking patients if they felt stressed easily, had mood swings, and whether they felt in control of their lives while tiredness was assessed by asking if they had been tired, had difficulty in being motivated to do anything at all, and whether they felt energetic.

These were marked on a scale of 0 to 4 by the patients, with 0 being not at all to 4 being very much (5 point Likert scale).

The least affected domain was that of hypothyroidism symptoms. As only one patient in this cohort had hypothyroidism this finding may not be representative.

The other less affected domains were eye symptoms, cognitive symptoms, and impaired social and daily life. In addition, there was a significant difference ($p \leq 0.001$) in the composite pre operative score compared to the postoperative score. Similar results were witnessed in literature, as evidenced by a prospective case series in Denmark using the ThyPRO questionnaire administered three and six months post operatively (30).

The impact of other objective parameters that could have influenced the postoperative change in quality of life was also evaluated. On Univariate analysis, age less than 40 years and female

gender were significantly associated ($p \leq 0.001$) with improved postoperative quality of life. However, both these parameters were not significant on the multivariate analysis. This was compared to international literature, which also showed less relief in goitre symptoms with increasing age and more relief experienced by female patients (30).

Another section of the analysis compared each of these variables with the domains in the ThyPRO 39 questionnaire, to assess which variables affected particular domains more than the others by a bivariate regression analysis. In the study population, the age group of less than 40 years experienced more symptoms of tiredness and emotional symptoms (p-values of 0.030 and 0.029 respectively). The Indian study by Mishra et al had shown a significant association with nervousness and age less than 50 years.

Tiredness, depression and anxiety were significant in females ($p = 0.029$, 0.037, and 0.007 respectively). Mishra et al had shown significant association of female gender with fatigue.

Other variables like hyperthyroidism, hypocalcaemia, the type of goitre, duration of symptoms, and weight of the thyroidectomy specimen did not have a bearing on any particular domain.

Thus using this well recognized and thoroughly validated research tool – the ThyPRO 39 questionnaire, this study could demonstrate a profound improvement in quality of life post thyroidectomy. This information may aid the clinician and the patient while choosing operative management over other conservative approaches, and thus play a role in the decision making process.

8. Conclusion

A significant improvement ($p \leq 0.001$) in the quality of life following thyroid surgery for benign goitres in all domains except depression has been depicted in this cohort. The domains causing the most impairment in the preoperative quality of life were emotional symptoms and tiredness. Neither did age, gender, type of goitre, functional status, duration of symptom, weight/dimension of the gland nor did postoperative hypocalcaemia have any impact on the change in quality of life following thyroidectomy.

9. Limitations

We faced a few limitations in the course of this study, which we would like to improvise on in the subsequent studies. The main limitations are described below:-

1) The representation of patients with different functional status of the thyroid was not representative. There was only one patient with hypothyroidism in the entire cohort.
2) Considering the large group of patients who seek care at our high volume centre, the quality of life perception is bound to show differences across cultures, ethnicities and different socioeconomic strata.
3) A larger sample size may have limited the skewed variables.
4) This study aimed to assess improvement in quality of life post operatively. However, to offer a patient the choice between various modalities, it is imperative to compare quality of life improvement following each modality of treatment to be able to truly confirm the best treatment feasible in that clinical setting.
5) The results of this study would have been more uniform if all the operations were done by the same surgeon, or consultants with uniform experience and skills.

10. References

1. BĂRBUȘ E, PEȘTEAN C, LARG MI, PICIU D. Quality of life in thyroid cancer patients: a literature review. Clujul Med. 2017;90(2):147–53.

2. Vanderpump MPJ. The epidemiology of thyroid disease. Br Med Bull. 2011 Sep 1;99(1):39–51.

3. Unnikrishnan AG, Kalra S, Sahay RK, Bantwal G, John M, Tewari N. Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. Indian J Endocrinol Metab. 2013;17(4):647–52.

4. Marwaha RK, Tandon N, Ganie MA, Kanwar R, Sastry A, Garg MK, et al. Status of thyroid function in Indian adults: two decades after universal salt iodization. J Assoc Physicians India. 2012 Apr;60:32–6.

5. Bajwa SJS, Sehgal V. Anesthesia and thyroid surgery: The never ending challenges. Indian J Endocrinol Metab. 2013;17(2):228–34.

6. Loyo M, Tufano RP, Gourin CG. National trends in thyroid surgery and the effect of volume on short-term outcomes: Volume-Based Trends in Thyroid Surgery. The Laryngoscope. 2013 Aug;123(8):2056–63.

7. Niazi AK, Kalra S, Irfan A, Islam A. Thyroidology over the ages. Indian J Endocrinol Metab. 2011 Jul;15(Suppl2):S121–6.

8. Sarkar S, Banerjee S, Sarkar R, Sikder B. A Review on the History of 'Thyroid Surgery.' Indian J Surg. 2016 Feb;78(1):32–6.

9. Oertli D. 7 Technique of Thyroidectomy. :9.

10. Margolick J, Wiseman SM. Risk of major complications following thyroidectomy and parathyroidectomy: Utility of the NSQIP surgical risk calculator. Am J Surg. 2018 May 1;215(5):936–41.

11. Caulley L, Johnson-Obaseki S, Luo L, Javidnia H. Risk factors for postoperative complications in total thyroidectomy. Medicine (Baltimore) [Internet]. 2017 Feb 3 [cited 2018 Jul 29];96(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5293415/

12. Ernandes Neto M, Tagliarini JV, López BE, Padovani CR, Marques M de A, Castilho EC, et al. Factors influencing thyroidectomy complications. Braz J Otorhinolaryngol. 2012 Jun;78(3):63–9.

13. WHO | WHOQOL: Measuring Quality of Life [Internet]. WHO. [cited 2018 Jul 17]. Available from: http://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/

14. Watt T, Barbesino G, Bjorner JB, Bonnema SJ, Bukvic B, Drummond R, et al. Cross-cultural validity of the thyroid-specific quality-of-life patient-reported outcome measure, ThyPRO. Qual Life Res. 2015 Mar 1;24(3):769–80.

15. Watt T, Cramon P, Hegedüs L, Bjorner JB, Bonnema SJ, Rasmussen ÅK, et al. The Thyroid-Related Quality of Life Measure ThyPRO Has Good Responsiveness and Ability to Detect Relevant Treatment Effects. J Clin Endocrinol Metab. 2014 Oct 1;99(10):3708–17.

16. Mintziori G, Watt T, Veneti S, Panagiotou A, Pournaras DJ, Feldt-Rasmussen U, et al. ThyPROgr: the Greek edition of the ThyPRO questionnaires for patients with benign thyroid diseases. Hormones. 2018 Mar 1;17(1):107–12.

17. Watt T, Bjorner JB, Groenvold M, Cramon P, Winther KH, Hegedüs L, et al. Development of a Short Version of the Thyroid-Related Patient-Reported Outcome ThyPRO. Thyroid Off J Am Thyroid Assoc. 2015 Oct;25(10):1069–79.

18. Wong CKH, Choi EPH, Woo YC, Lang BHH. Measurement properties of ThyPRO short-form (ThyPRO-39) for use in Chinese patients with benign thyroid diseases. Qual Life Res Int J Qual Life Asp Treat Care Rehabil. 2018 Aug;27(8):2177–87.

19. Mishra A, Sabaretnam M, Chand G, Agarwal G, Agarwal A, Verma AK, et al. Quality of life (QoL) in patients with benign thyroid goiters (pre- and post-thyroidectomy): a prospective study. World J Surg. 2013 Oct;37(10):2322–9.

20. Thakkar DB, Deshmukh SD, Akhtar M. Nontoxic goiter: causes, clinical evaluation and management. Int Surg J. 2018 Apr 21;5(5):1873–7.

21. Järhult J, Vedad R. A Conservative Approach Is Reasonable in Patients with Non-Toxic Goitre: Results from an Observational Study during 30 Years. Eur Thyroid J. 2014;3(4):240–4.

22. Zheng L, Yan W, Kong Y, Liang P, Mu Y. An epidemiological study of risk factors of thyroid nodule and goiter in Chinese women. Int J Clin Exp Med. 2015 Jul 15;8(7):11379–87.

23. K. Bartsch D, Luster M, J. Buhr H, Lorenz D, Germer C-T, E. Goretzki P. Indications for the Surgical Management of Benign Goiter in Adults. Dtsch Ärztebl Int. 2018 Jan;115(1–2):1–7.

24. Vassiliou I, Tympa A, Arkadopoulos N, Nikolakopoulos F, Petropoulou T, Smyrniotis V. Total thyroidectomy as the single surgical option for benign and malignant thyroid disease: a surgical challenge. Arch Med Sci AMS. 2013 Feb 21;9(1):74–8.

25. Dodiyi-Manuel A, Dodiyi-Manuel ST. Spectrum of thyroid diseases in the surgical department of a tertiary centre in South-south, Nigeria. Niger Health J [Internet]. 2016 Jan 1 [cited 2018 Sep 25];16(2). Available from: https://www.ajol.info/index.php/nhj/article/view/149478

26. Noureldine SI, Genther DJ, Lopez M, Agrawal N, Tufano RP. Early predictors of hypocalcemia after total thyroidectomy: an analysis of 304 patients using a short-stay monitoring protocol. JAMA Otolaryngol-- Head Neck Surg. 2014 Nov;140(11):1006–13.

27. Wu J, Harrison B. Hypocalcemia after Thyroidectomy: The Need for Improved Definitions. Agarwal A, editor. World J Endocr Surg. 2010 Jan;17–20.

28. Nair CG, Babu MJC, Menon R, Jacob P. Hypocalcaemia following total thyroidectomy: An analysis of 806 patients. Indian J Endocrinol Metab. 2013 Mar 1;17(2):298.

29. RULLI F, AMBROGI V, DIONIGI G, AMIRHASSANKHANI S, MINEO TC, OTTAVIANI F, et al. Meta-analysis of recurrent laryngeal nerve injury in thyroid surgery with or without intraoperative nerve monitoring. Acta Otorhinolaryngol Ital. 2014 Aug;34(4):223–9.

30. Sorensen JR. The impact of surgery on quality of life, esophageal motility, and tracheal anatomy and airflow in pa- tients with benign nodular goiter. :20.

ANNEXURE – 1

PATIENT PERFORMA

SERIAL NUMBER

NAME

AGE

GENDER

ADDRESS

TELEPHONE NUMBERS

E MAIL ID

METHOD OF QUESTIONNAIRE FILLING

PREOPERATIVELY

POSTOPERATIVELY

DATE OF ENROLMENT

DATE OF SUBMISSION OF QUESTIONNAIRE POST OPERATIVELY

DURATION

HORMONAL DYSFUNCTION [Y/N]

DURATION OF HORMONAL DYSFUNCTION

TYPE OF GOITER

RETROSTERNAL EXTENSION [Y/N]

INDICATION FOR SURGERY

DATE OF SURGERY

TYPE OF SURGERY

FNAC FINDING

MEAN SPECIMEN WEIGHT

DIMENSION OF GOITER

PATHOLOGY

POST OPERATIVE HYPOCALCEMIA [Y/N]

POST OPERATIVE RLN PALSY [Y/N]

PATIENT INFORMATION SHEET

You are being asked to enroll in a study that aims to assess quality of life before and after operation for benign goiters. Please take time to read/listen to the following information. The study personnel will be available to answer questions/clarifications that you may have in this regard.

Description of the study

The study aims to assess the quality of life in patients with benign goiters. This will be done using a questionnaire which will be given on the day before the operation. The questionnaire is a means of looking at the physical, mental and social aspects of quality of life in benign goiters.

The same questionnaire will be given to you six months after the operation, either during follow up in the OPD or by means of mail or telephonic conversation. The assessment done by you six months after surgical removal of the benign goiter will be compared to the quality of life before the operation. This will help us realize if the operation has helped in improving quality of life or not.

We will also be looking at the influence of factors which have a bearing on quality of life, like the weight of the goiter, and the pathology, etc. This is just to help us know how much the quality of life can be influenced by other factors.

Your decision to participate in this study is entirely voluntary. Your decision will not create a bias for/against you in terms of your medical care or operation. Please feel free to clarify any doubts before you decide to participate in this study.

Advantages/ benefits of being enrolled in the study

There are no immediate benefits of participating in this study. There will be no change in the treatment provided by your treating surgeon. There will be no monetary benefits for enrolling. The results of this study will help doctors offer the best option to improve quality of life to patients in the future. The patients will get to choose between treatment options knowing if operation for benign goiters will significantly improve quality of life or not. If operation for benign goiters does not seem to enhance quality of life after the operation, then it will take a lower position among the various modalities of treating the same.

Foreseeable risks/ inconveniences

Since this is only a questionnaire based study, no obvious risks or inconveniences are expected.

Study participation withdrawal

You are voluntarily deciding to participate in this study. If at some point of time you decide to

withdraw from the study, there will be no compromise of care from our side, or any loss of benefits.

Confidentiality of the data collected

The information collected will remain strictly confidential. It is information that is protected by the research personnel and will not be disclosed.

In addition to the information provided above, if you need to clarify any further doubts, kindly contact:

Dr. Swarna Azaria

Surgery unit 1

Department of General Surgery

CMC Vellore

9945941150

swarna.azaria@gmail.com

INFORMED CONSENT FORM

Study Title:

QUALITYOF LIFE POST THYROIDECTOMY IN PATIENTS

WITH BENIGN GOITERS

Informed Consent form to participate in a research study

Study Number: _____

Subject's

Initials: _____

Subject's Name: _____

_____

Hospital Number: _____

Date of Birth / Age: _____

Address and Phone Number: _____

_____

Phone:

_____

I confirm that I have read and understood the information sheet dated _____ for the

above study and have had the opportunity to ask questions.

I understand that my participation in the study is voluntary and that I am free to withdraw at any

time, without giving any reason, without my medical

care or legal rights being affected. I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that

may be conducted in relation to it, even if I withdraw from the trial. I agree to this access.

However, I understand that my identity will not be revealed in any information released to third parties or published.

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date:

_____/_____/_____

Signatory's Name: _____ :

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the

Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

DATA SHEET

sno	name	age	gender	hospno	dursym	durhor	hortype	type	rsext	ind
1	karuna	34	2	820811g	6	0	3	4	2	1
2	jahangir	53	1	184593d	24	0	3	1	2	1
3	sunita	29	2	857429g	120	24	2	3	2	2
4	dipti	36	2	913173g	36	0	3	2	2	1
5	janaki	41	2	215889g	36	0	3	1	2	1
6	aditi	26	2	800456g	48	48	2	3	2	2
7	natabar	45	1	425988g	180	0	3	1	2	1
8	tapasi	52	2	807098g	36	0	3	2	2	1
9	dilip	41	1	900895g	36	0	3	2	2	1
10	heena	38	2	381777g	36	0	3	1	2	1
11	kabita	34	2	914383g	6	5	2	3	2	2
12	chinmoy	40	1	848796g	96	0	3	2	2	1
13	suman	33	2	870333g	60	0	3	1	2	1
14	mohan	54	1	374446g	48	48	2	3	2	2
15	rupa	33	2	652773g	36	0	3	2	2	1
16	soma	35	2	371308g	36	36	2	3	2	2
17	jai narayan	67	1	884349d	4	0	3	2	2	1
18	mst soma	50	2	783466g	48	24	2	3	2	2
19	gopinath	67	1	799679b	15	0	3	1	2	1
20	dasarani	58	2	808068d	120	0	3	2	2	4
21	chandana	37	2	788525g	60	0	3	1	2	1
22	manasi	25	2	670518g	60	0	3	1	2	1
23	sanjaya	34	1	123584g	24	24	1	2	2	4
24	rama	56	2	923811b	48	48	2	3	2	2
25	grishma	26	2	073118h	12	0	3	1	2	4
26	loganayaki	52	2	347901b	36	0	3	1	2	1
27	latha	36	2	391408g	120	120	2	3	2	2
28	srabani	48	2	963607c	144	0	3	2	2	1
29	asma	52	2	678645g	48	48	2	3	2	2
30	arumugam	52	1	197391f	12	0	3	1	2	3
31	rajumari	50	2	812962g	120	0	3	2	2	1
32	bijjala	24	2	128028h	48	0	3	1	2	1
33	sidartha	39	1	832657f	36	0	3	2	2	1
34	ananda	36	1	701996g	72	0	3	1	2	1
35	kunjumol	60	2	858742g	6	0	3	2	2	1
36	subramani	52	1	764061g	36	0	3	2	2	1
37	jumpa	29	2	785359g	12	0	3	2	2	3
38	divya	19	2	566825b	48	0	3	1	2	1
39	swati	29	2	768640g	72	0	3	3	2	1

40	chitra	47	2	958200g	48	0	3	2	2	1
41	girja	51	2	783444g	120	0	3	2	2	3
42	sushil	58	1	749171g	1	0	3	2	2	1
43	mohan	53	1	374446g	48	48	2	3	2	2
44	leena	54	2	463718f	36	36	2	1	2	2
45	chaitali	43	2	904240g	36	0	3	2	2	1
46	pown	52	1	820618g	12	10	2	2	2	2
47	tara	50	2	776125g	6	0	3	2	2	1
48	sharmila	44	2	897242g	36	0	3	2	2	3
49	sushma	36	2	870752g	84	0	3	2	2	1
50	mohan	55	1	897819b	5	0	3	2	2	1

datesur	typesur	fnac	weight	dimen	path	hypocal	rlnpalsy	pre1a
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########	1	1	100	2	3	2	2	3
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########	1	1	50	1	1	2	2	0
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pre1x	pre1bb	pre2a	pre2c	pre3b	pre4a	pre4b	pre4f	pre5b	pre5c	pre5e	pr
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pre6a	pre6e	pre6g	pre7c	pre7d	pre7h	pre8a	pre8b	pre8c	pre9a	pre9c
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3	3	3	3	3	4	0	0	0	0	0
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0	0	3	0	0	3	0	0	0	0	0

pre9e	pre11a	pre11d	pre11e	pre12	post1a	post1c	post1h	post1l	post1m	post1n
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2	2	1	0	2	0	0	0	0	0	0
1	1	0	0	1	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
0	2	2	2	2	0	0	0	0	0	0
2	2	0	0	2	0	0	0	1	1	1
2	1	0	0	1	0	0	0	0	0	0
4	4	4	4	3	0	0	0	3	0	1
2	1	0	0	1	0	0	0	0	0	0
2	2	2	0	2	1	1	1	0	0	0
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	3	0	0	0	0	1	1
0	3	3	3	1	0	0	0	0	0	0
0	1	0	0	0	0	1	1	0	0	0
3	1	1	0	2	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
2	2	2	0	1	0	0	0	0	0	0
2	2	1	1	2	0	0	0	1	2	0
0	2	2	2	1	0	0	0	0	0	0
0	1	1	0	1	0	0	0	0	0	0
0	1	0	0	1	0	0	0	0	1	0

2	2	0	0	1	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
0	3	1	0	2	0	0	0	0	0	0
1	2	2	1	1	0	0	0	0	0	0
0	1	0	0	1	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	1	0	0	0	0	1	0
0	1	2	0	1	0	0	0	0	0	0
0	2	1	1	1	0	0	0	0	0	0
0	0	0	0	1	0	0	0	0	0	0

post1t	post1q	post1cc	post1dd	post1ee	post1w	post1x	post1bb	post2a	post2c	post3b
0	0	0	0	0	0	0	0	3	2	2
0	0	0	0	0	1	0	0	0	0	4
0	0	0	0	0	0	0	0	1	1	3
0	0	0	0	0	0	0	0	1	1	3
0	0	0	0	0	0	1	0	1	1	3
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	1	0	3
0	0	0	0	0	0	0	0	3	2	2
0	0	0	0	0	0	0	0	2	1	3
0	0	0	0	0	0	0	0	1	0	4
0	0	0	0	0	0	0	0	0	0	3
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	1	1	3
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	3
2	0	0	0	0	0	0	0	1	1	3
0	2	0	1	0	0	0	1	2	2	3
0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	1	1	4
1	0	0	0	0	0	1	0	1	1	3
0	0	0	0	0	0	0	0	1	0	3
0	0	0	0	0	0	0	0	4	4	1
0	0	0	0	0	1	1	0	1	1	3
0	1	0	2	1	0	1	1	1	1	3
0	0	0	0	0	0	1	0	0	0	4
0	0	0	0	0	0	0	1	1	1	3
0	1	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	1	2	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	1	0	1	1	3
0	0	0	0	0	0	1	0	0	0	4
0	0	0	0	0	0	0	0	1	0	4
0	0	0	0	0	0	0	0	0	0	4

0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	1	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	3
0	0	0	0	0	0	0	0	2	0	3
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4
0	0	0	0	0	0	0	0	0	0	4

post4a	post4b	post4f	post5b	post5c	post5e	post6a	post6e	post6g	post7c	post7d
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	1	1	0	1	1	1	3	1	1
1	0	0	1	1	1	1	1	4	1	1
0	0	0	0	0	0	1	1	4	1	1
0	0	0	1	0	0	1	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
1	0	1	0	0	0	0	0	4	0	1
0	0	0	0	0	0	0	0	4	0	1
1	0	0	0	0	0	0	0	4	0	0
0	0	0	0	1	0	0	0	4	1	0
0	0	0	1	1	1	0	0	4	1	1
0	0	0	0	0	0	0	0	4	0	1
0	0	0	0	0	0	0	0	4	0	1
0	0	0	0	0	0	0	0	4	0	1
0	0	0	0	0	0	0	0	4	0	0
0	0	0	1	1	1	1	1	4	1	1
0	0	0	0	0	0	0	0	4	1	1
0	0	0	0	0	0	0	0	3	0	0
0	0	0	1	1	1	1	1	4	1	1
1	0	2	2	2	2	1	0	4	1	1
1	0	0	0	0	0	0	0	4	0	1
0	0	0	1	0	0	1	1	4	1	1
1	1	1	1	1	1	1	1	3	1	1
0	0	0	0	0	0	0	0	4	0	0
0	0	0	2	3	3	2	2	2	3	3
0	0	0	0	0	0	0	0	4	0	2
1	0	0	0	1	1	1	1	3	1	1
1	0	0	0	1	0	0	0	4	1	0
0	0	0	2	1	1	1	1	4	2	2
0	0	0	0	0	0	0	0	4	0	2
0	0	0	0	0	0	0	0	4	2	2
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	1	1	3	1	1
0	0	0	0	0	0	0	0	4	1	0
0	0	0	0	0	0	0	0	4	1	1
0	0	0	0	0	0	0	0	4	0	0

0	0	0	1	1	1	1	1	4	1	1
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0
0	0	0	0	0	0	0	0	4	0	0

post7h	post8a	post8b	post8c	post9a	post9c	post9e	post11a	post11d	post11e	post12
4	0	0	0	1	0	0	0	0	0	1
4	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	1	1	0	0	0	1
4	0	0	0	0	0	0	0	0	0	1
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	1	0	1	0	0	0	1
4	0	0	0	0	0	0	0	0	0	1
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	1	0	0	0	0
4	0	0	0	1	0	1	0	0	0	1
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	1	0	0	0	1
4	0	0	0	0	0	0	0	0	0	0
3	1	0	0	0	0	0	3	3	3	3
4	0	0	0	0	0	1	2	0	0	0
4	0	0	0	0	0	0	0	0	0	1
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	1
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	1	0	0	0

4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0

Scale content of the ThyPRO-39

The twelve ThyPRO-39 scales consist of the following items, summarized within each scale to form a scale score for each scale ranging 0-100 (cf. separate scoring instruction).

Goitre symptoms

During the past 4 weeks have you

1a - had the sensation of fullness in the neck?

1c - felt pressure in your throat?

1h - felt discomfort swallowing?

Hyperthyroid symptoms:

During the past 4 weeks have you

1l - had trembling hands?

1m - had a tendency to sweat a lot?

1n - experienced palpitations (rapid heart beat)?

1t - had an upset stomach?

Hypothyroid symptoms:

During the past 4 weeks have you

1q - been sensitive to cold?

1cc - had swollen hands or feet?

1dd - had dry skin?

1ee - had itchy skin?

Eye symptoms:

During the past 4 weeks have you

1w - had the sensation of dryness or “grittiness” in the eyes?
1x - had impaired vision?
1bb - been very sensitive to light?

Tiredness:

During the past 4 weeks have you

2a - been tired?
2c - had difficulty getting motivated to do anything at all?
3b - felt energetic?*

Cognitive problems:

During the past 4 weeks have you

4a - had difficulty remembering?
4b - had slow or unclear thinking?
4f - had difficulty concentrating?

Anxiety:

During the past 4 weeks have you

5b - felt afraid or anxious?
5c - felt tense?
5e - felt uneasy?

Depressivity:

During the past 4 weeks have you

6a - felt sad?

6e - felt unhappy?

6g - had self-confidence?*

Emotional Susceptibility:

During the past 4 weeks have you

7c - noticed you easily felt stressed?

7d - had mood swings?

7h - felt in control of your life?*

Impaired Social life:

During the past 4 weeks, <u>has your thyroid disease caused</u> you to

8a - have difficulty being together with other people (for example, spouse, children, boy/girlfriend, friends, or others)?

8b - feel you were a burden to other people?

8c - have conflicts with other people?

Impaired Daily life:

During the past 4 weeks, <u>has your thyroid disease caused</u> you to

9a - have difficulty managing your daily life?

9c - not be able to participate in life around you?

9e - feel as if everything takes longer to do?

Cosmetic Complaints:

During the past 4 weeks

11a - has your thyroid disease affected your appearance (for example, swelling of the neck, eye changes, weight changes)?

11d - have you been bothered by other people looking at you?

11e - has your thyroid disease influenced which clothes you wear?

In addition, ThyPRO contains one item not included in any multi-item scale:

During the past 4 weeks

12 - has your thyroid disease had a negative effect on your quality of life?

*Positively worded items are scored reversely when constructing scales

Scoring of the ThyPRO-39 questionnaire

Each of the 13 ThyPRO-39 scales is scored as a summary score and transformed to range 0-100. This scoring procedure is described step by step below.

Naming of items

Each item is named TQ{relevant itemnumber}. Itemnumber is indicated left of each item in the questionnaire. Thus, the first item, 'sensation of fullness in the neck' is named TQ1A in the database.

Scoring of responses

Item responses are scored

0 for 'Not at all'

1 for 'A little'

2 for 'Some'

3 for 'Quite a bit'

4 for 'Very much'/'Completely'

Scale content

Each scale consists of the following items:

Goitre symptoms scale: TQ1A TQ1C TQ1H;

Hyperthyroid symptoms scale: TQ1l TQ1M TQ1N TQ1T;

Hypothyroid symptoms scale: TQ1Q TQ1CC TQ1DD TQ1EE;

Eye symptoms scale: TQ1W TQ1X TQ1BB;

Tiredness scale: TQ2A TQ2C TQ3B;

Cognitive problems scale: TQ4A TQ4B TQ4F;

Anxiety scale: TQ5B TQ5C TQ5E;

Depressivity scale: TQ6A TQ6E TQ6G;

Emotional Susceptibility scale: TQ7C TQ7D TQ7H;

Impaired Social life scale: TQ8A TQ8B TQ8C;

Impaired Daily life scale: TQ9A TQ9C TQ9E;

Cosmetic Complaints scale: TQ11A TQ11D TQ11E;

Overall QoL: TQ12

Scoring the individual scales

In principle, scales are scored by simply adding the response values (0-4) for all the items in a scale. However, three additional features expand this procedure: reversal of positively worded items, imputation for individual missing item responses and 0-100 transformation.

Reversal of positively worded items

As part of the scoring procedure, items 3B, 6G and 7H have to be reversed, i.e. 'Not at all' scored as 4, 'A little' as 3, 'Some' as 2, 'Quite a bit' as 1 and 'Very much'/'Completely scored as 0.

Imputation for individual missing items

If half or more of the items in a scale is completed, missing items are substituted by the mean of the completed items.

Linear transformation

All scales (except for the Hypothyroid Symptoms and the Overall QoL scale, see below) are transformed linearly to range 0-100 according to Table 1 below:

Table 1. To the left is the raw score. The corresponding 0-100 score is tabulated for each scale separately. For example, a patient with a raw score on the Goiter Symptoms scale of 6 (e.g. because she answered “Some” to all three Goiter items), will have a 0-100 Goiter Symptoms score of 37. A raw score of 6 on the Tiredness scale, would yield a 0-100 score of 50.

Raw sum score	**Final rescaled short-form score**										
	Goiter	Hyper	Eye	Tired	Cogni-tion	Anxiety	Depres-sion	Suscep-tibility	Social Life	Daily Life	Appear-ance
0	2	2	1	0	1	1	0	1	0	0	1
1	10	8	8	8	7	10	7	7	8	7	12
2	15	13	14	17	14	18	14	13	17	15	21
3	20	18	20	25	21	26	22	21	25	22	28
4	26	23	25	33	29	34	29	28	33	30	36
5	31	28	32	42	37	41	37	36	42	38	43
6	37	33	38	50	44	49	45	44	50	46	51
7	43	38	45	58	52	56	54	52	58	54	59
8	49	44	52	67	60	63	63	60	67	62	66
9	57	49	60	75	68	71	71	68	75	71	73
10	64	55	68	83	76	79	80	77	83	80	80
11	73	60	78	92	85	87	89	86	92	89	87
12	84	66	89	100	95	96	97	95	100	98	96
13		71									
14		77									
15		84									
16		90									

Transformation of the Hypothyroid Symptoms scale:

The ThyPRO-39 Hypothyroid Symptoms is identical to the original ThyPRO Hypothyroid Symptoms scale and is thus transformed to 0-100 according to the formula

Transformed score=(raw sumscore/16)*100

For example, if a patient answered 'Not at all' to two items, 'A little' to one item and 'Some' to the last item, she would have a raw score of **3** (0+0+1+2). The transformed 0-100 score would then be 3/16*100=**19**.

Transformation of the Overall QoL-impact scale/item:

The Overall QoL item (TQ12) is rescaled to 0-100 simply by taking the mean raw score and multiply by 25.

Scoring the Composite scale

The Composite scale is based on the 22 items from the Tiredness, Cognition, Anxiety, Depressivity, Emotional Susceptibility, Impaired Social life Impaired Daily Life and Overall QoL scales:

TQ2A TQ2C TQ3B TQ4A TQ4B TQ4F TQ5B TQ5C TQ5E TQ6A TQ6E TQ6G TQ7C TQ7D TQ7H TQ8A TQ8B TQ8C TQ9A TQ9C TQ9E TQ12

The raw score is derived as described above, by summation (with imputation for missing), to range 0-88. The raw score is transformed to 0-100 according to the formula

Transformed score=(raw sumscore/88)*100

SAS code

The following SAS code performs this scale scoring, when inserted into a SAS data step:

```
*=============================================================================================
ThyPRO-39 Goitre symptoms scale (Goitre39)
*---------------------------------------------------------------------------------------------;
If n (of tq1a tq1c tq1h) gt 1 then
RawGoitre39 =mean(tq1a, tq1c, tq1h) *3;

Goitre39= (0 le RawGoitre39 lt 0.5)*2+
          (0.5 le RawGoitre39 lt 1.5)*10+
          (1.5 le RawGoitre39 lt 2.5)*15+
          (2.5 le RawGoitre39 lt 3.5)*20+
          (3.5 le RawGoitre39 lt 4.5)*26+
          (4.5 le RawGoitre39 lt 5.5)*31+
          (5.5 le RawGoitre39 lt 6.5)*37+
          (6.5 le RawGoitre39 lt 7.5)*43+
          (7.5 le RawGoitre39 lt 8.5)*49+
          (8.5 le RawGoitre39 lt 9.5)*57+
          (9.5 le RawGoitre39 lt 10.5)*64+
          (10.5 le RawGoitre39 lt 11.5)*73+
          (11.5 le RawGoitre39 lt 12.5)*84+
           Rawgoitre39-Rawgoitre39
;


Label Goitre39 = 'ThyPRO-39 Goitre symptoms Scale';


*---------------------------------------------------------------------------------------------
ThyPRO-39 Hyperthyroid symptoms scale (Hyper39)
*---------------------------------------------------------------------------------------------;
If n (of tq1l tq1m tq1n tq1t) gt 1 then
RawHyper39 =mean(tq1l, tq1m, tq1n, tq1t) *4;

Hyper39= (0 le RawHyper39 lt 0.5)*2+
         (0.5 le RawHyper39 lt 1.5)*8+
         (1.5 le RawHyper39 lt 2.5)*13+
         (2.5 le RawHyper39 lt 3.5)*18+
         (3.5 le RawHyper39 lt 4.5)*23+
         (4.5 le RawHyper39 lt 5.5)*28+
         (5.5 le RawHyper39 lt 6.5)*33+
         (6.5 le RawHyper39 lt 7.5)*38+
         (7.5 le RawHyper39 lt 8.5)*44+
         (8.5 le RawHyper39 lt 9.5)*49+
         (9.5 le RawHyper39 lt 10.5)*55+
         (10.5 le RawHyper39 lt 11.5)*60+
         (11.5 le RawHyper39 lt 12.5)*66+
         (12.5 le RawHyper39 lt 13.5)*71+
         (13.5 le RawHyper39 lt 14.5)*77+
         (14.5 le RawHyper39 lt 15.5)*84+
         (15.5 le RawHyper39 lt 16.5)*90+
          RawHyper39-RawHyper39
;

Label Hyper39 = 'ThyPRO-39 Hyperthyroid symptoms Scale';

*---------------------------------------------------------------------------------------------
ThyPRO-39 Hypothyroid symptoms scale (Hypo39)
*---------------------------------------------------------------------------------------------;
if n (of TQ1Q TQ1CC TQ1DD TQ1EE) gt 1 then
Hypo39 = 100*(mean(TQ1Q, TQ1CC, TQ1DD, TQ1EE))/4;
```

```
Label Hypo39 = 'ThyPRO-39 Hypothyroid symptoms Scale';

*-------------------------------------------------------------------------------------------
ThyPRO-39 Eye symptoms scale (Eye39)
*-------------------------------------------------------------------------------------------;
if n (of tq1w tq1x tq1bb) gt 1 then
RawEye39 = mean(tq1w, tq1x, tq1bb)*3;

Eye39=     (0 le RawEye39 lt 0.5)*1+
           (0.5 le RawEye39 lt 1.5)*8+
           (1.5 le RawEye39 lt 2.5)*14+
           (2.5 le RawEye39 lt 3.5)*20+
           (3.5 le RawEye39 lt 4.5)*25+
           (4.5 le RawEye39 lt 5.5)*32+
           (5.5 le RawEye39 lt 6.5)*38+
           (6.5 le RawEye39 lt 7.5)*45+
           (7.5 le RawEye39 lt 8.5)*42+
           (8.5 le RawEye39 lt 9.5)*60+
           (9.5 le RawEye39 lt 10.5)*68+
           (10.5 le RawEye39 lt 11.5)*78+
           (11.5 le RawEye39 lt 12.5)*89+
            RawEye39-RawEye39
;

Label Eye39 = 'ThyPRO-39 Eye symptoms Scale';

*-------------------------------------------------------------------------------------------
ThyPRO-39 Tiredness scale (Tired39)
*-------------------------------------------------------------------------------------------;
if n (of tq2a tq2c tq3b) gt 1 then
RawTired39 = mean(tq2a, tq2c, 4-tq3b)*3;

Tired39=   (0 le RawTired39 lt 0.5)*0+
           (0.5 le RawTired39 lt 1.5)*8+
           (1.5 le RawTired39 lt 2.5)*17+
           (2.5 le RawTired39  lt 3.5)*25+
           (3.5 le RawTired39  lt 4.5)*33+
           (4.5 le RawTired39  lt 5.5)*42+
           (5.5 le RawTired39  lt 6.5)*50+
           (6.5 le RawTired39  lt 7.5)*58+
           (7.5 le RawTired39  lt 8.5)*67+
           (8.5 le RawTired39  lt 9.5)*75+
           (9.5 le RawTired39  lt 10.5)*83+
           (10.5 le RawTired39  lt 11.5)*92+
           (11.5 le RawTired39  lt 12.5)*100+
           RawTired39-RawTired39
;

Label Tired39 = 'ThyPRO-39 Tiredness Scale';

*-------------------------------------------------------------------------------------------
ThyPRO-39 Cognitive problems scale (Cognition39)
*-------------------------------------------------------------------------------------------;
if n (of tq4a tq4b tq4f) gt 1 then
RawCognition39 = mean(tq4a, tq4b, tq4f)*3;

Cognition39=(0 le RawCognition39 lt 0.5)*1+
            (0.5 le RawCognition39 lt 1.5)*7+
            (1.5 le RawCognition39 lt 2.5)*14+
            (2.5 le RawCognition39  lt 3.5)*21+
            (3.5 le RawCognition39  lt 4.5)*29+
            (4.5 le RawCognition39  lt 5.5)*37+
            (5.5 le RawCognition39  lt 6.5)*44+
            (6.5 le RawCognition39  lt 7.5)*52+
            (7.5 le RawCognition39  lt 8.5)*60+
```

```
            (8.5 le RawCognition39  lt 9.5)*68+
            (9.5 le RawCognition39  lt 10.5)*76+
            (10.5 le RawCognition39  lt 11.5)*85+
            (11.5 le RawCognition39  lt 12.5)*95+
             RawCognition39-RawCognition39
;

Label Cognition39 = 'ThyPRO-39 Cognitive problems Scale';

*-------------------------------------------------------------------------------------
ThyPRO-39 Anxiety scale (Anxiety39)
*-------------------------------------------------------------------------------------;
if n (of tq5b tq5c tq5e) gt 1 then
RawAnxiety39 = mean(tq5b, tq5c, tq5e)*3;

Anxiety39=(0 le RawAnxiety39 lt 0.5)*1+
          (0.5 le RawAnxiety39 lt 1.5)*10+
          (1.5 le RawAnxiety39 lt 2.5)*18+
          (2.5 le RawAnxiety39  lt 3.5)*26+
          (3.5 le RawAnxiety39  lt 4.5)*34+
          (4.5 le RawAnxiety39  lt 5.5)*41+
          (5.5 le RawAnxiety39  lt 6.5)*49+
          (6.5 le RawAnxiety39  lt 7.5)*56+
          (7.5 le RawAnxiety39  lt 8.5)*63+
          (8.5 le RawAnxiety39  lt 9.5)*71+
          (9.5 le RawAnxiety39  lt 10.5)*79+
          (10.5 le RawAnxiety39  lt 11.5)*87+
          (11.5 le RawAnxiety39  lt 12.5)*96+
          RawAnxiety39-RawAnxiety39
;

Label Anxiety39 = 'ThyPRO-39 Anxiety Scale';

*-------------------------------------------------------------------------------------
ThyPRO-39 Depressivity scale (Depress39)
*-------------------------------------------------------------------------------------;
if n (of tq6a tq6e tq6g) gt 1 then
RawDepress39 = mean(tq6a, tq6e, 4-tq6g)*3;

Depress39=(0 le RawDepress39 lt 0.5)*0+
          (0.5 le RawDepress39 lt 1.5)*7+
          (1.5 le RawDepress39 lt 2.5)*14+
          (2.5 le RawDepress39  lt 3.5)*22+
          (3.5 le RawDepress39  lt 4.5)*29+
          (4.5 le RawDepress39  lt 5.5)*37+
          (5.5 le RawDepress39  lt 6.5)*45+
          (6.5 le RawDepress39  lt 7.5)*54+
          (7.5 le RawDepress39  lt 8.5)*63+
          (8.5 le RawDepress39  lt 9.5)*71+
          (9.5 le RawDepress39  lt 10.5)*80+
          (10.5 le RawDepress39  lt 11.5)*89+
          (11.5 le RawDepress39  lt 12.5)*97+
           RawDepress39-RawDepress39
;

Label Depress39 = 'ThyPRO-39 Depressivity Scale';

*-------------------------------------------------------------------------------------
ThyPRO-39 Emotional Susceptibility scale (Suscept39)
*-------------------------------------------------------------------------------------;
if n (of tq7c tq7d tq7h) gt 1 then
RawSuscept39 = mean(tq7c, tq7d, 4-tq7h)*3;

Suscept39=(0 le RawSuscept39 lt 0.5)*1+
          (0.5 le RawSuscept39 lt 1.5)*7+
```

```
           (1.5 le RawSuscept39 lt 2.5)*13+
           (2.5 le RawSuscept39  lt 3.5)*21+
           (3.5 le RawSuscept39  lt 4.5)*28+
           (4.5 le RawSuscept39  lt 5.5)*36+
           (5.5 le RawSuscept39  lt 6.5)*44+
           (6.5 le RawSuscept39  lt 7.5)*52+
           (7.5 le RawSuscept39  lt 8.5)*60+
           (8.5 le RawSuscept39  lt 9.5)*68+
           (9.5 le RawSuscept39  lt 10.5)*77+
           (10.5 le RawSuscept39  lt 11.5)*86+
           (11.5 le RawSuscept39  lt 12.5)*95+
            RawSuscept39-RawSuscept39
;

Label Suscept39 = 'ThyPRO-39 Emotional Susceptibility Scale';
*-------------------------------------------------------------------------------------------
ThyPRO-39 Social Impairment scale (Social39)
*-------------------------------------------------------------------------------------------;
if n (of tq8a tq8b tq8c) gt 1 then
RawSocial39 = mean(tq8a, tq8b, tq8c)*3;

Social39=  (0 le RawSocial39 lt 0.5)*0+
           (0.5 le RawSocial39 lt 1.5)*8+
           (1.5 le RawSocial39 lt 2.5)*17+
           (2.5 le RawSocial39  lt 3.5)*25+
           (3.5 le RawSocial39  lt 4.5)*33+
           (4.5 le RawSocial39  lt 5.5)*42+
           (5.5 le RawSocial39  lt 6.5)*50+
           (6.5 le RawSocial39  lt 7.5)*58+
           (7.5 le RawSocial39  lt 8.5)*67+
           (8.5 le RawSocial39  lt 9.5)*75+
           (9.5 le RawSocial39  lt 10.5)*83+
           (10.5 le RawSocial39  lt 11.5)*92+
           (11.5 le RawSocial39  lt 12.5)*100+

            RawSocial39-RawSocial39
;

Label Social39 = 'ThyPRO-39 Social impairment Scale';

*-------------------------------------------------------------------------------------------
ThyPRO-39 Impaired Daylife scale (Daylife39)
*-------------------------------------------------------------------------------------------;
if n (of tq9a tq9c tq9e) gt 1 then
RawDaylife39 = mean(tq9a, tq9c, tq9e)*3;

Daylife39=(0 le RawDaylife39 lt 0.5)*0+
           (0.5 le RawDaylife39 lt 1.5)*7+
           (1.5 le RawDaylife39 lt 2.5)*15+
           (2.5 le RawDaylife39  lt 3.5)*22+
           (3.5 le RawDaylife39  lt 4.5)*30+
           (4.5 le RawDaylife39  lt 5.5)*38+
           (5.5 le RawDaylife39  lt 6.5)*46+
           (6.5 le RawDaylife39  lt 7.5)*54+
           (7.5 le RawDaylife39  lt 8.5)*62+
           (8.5 le RawDaylife39  lt 9.5)*71+
           (9.5 le RawDaylife39  lt 10.5)*80+
           (10.5 le RawDaylife39  lt 11.5)*89+
           (11.5 le RawDaylife39  lt 12.5)*98+

            RawDaylife39-RawDaylife39
;

Label Daylife39 = 'ThyPRO-39 Impaired Daylife Scale';
```

```
*-------------------------------------------------------------------------------------------
ThyPRO-39 Cosmetic Complaints scale (Cosmetic39)
*-------------------------------------------------------------------------------------------;
if n (of tq11a tq11d tq11e) gt 1 then
RawCosmetic39 = mean(tq11a, tq11d, tq11e)*3;

Cosmetic39= (0 le RawCosmetic39 lt 0.5)*1+
            (0.5 le RawCosmetic39 lt 1.5)*12+
            (1.5 le RawCosmetic39 lt 2.5)*21+
            (2.5 le RawCosmetic39  lt 3.5)*28+
            (3.5 le RawCosmetic39  lt 4.5)*36+
            (4.5 le RawCosmetic39  lt 5.5)*43+
            (5.5 le RawCosmetic39  lt 6.5)*51+
            (6.5 le RawCosmetic39  lt 7.5)*59+
            (7.5 le RawCosmetic39  lt 8.5)*66+
            (8.5 le RawCosmetic39  lt 9.5)*73+
            (9.5 le RawCosmetic39  lt 10.5)*80+
            (10.5 le RawCosmetic39  lt 11.5)*87+
            (11.5 le RawCosmetic39  lt 12.5)*96+

             RawCosmetic39-RawCosmetic39
;

Label Cosmetic39 = 'ThyPRO-39 Cosmetic Complaints Scale';

*-------------------------------------------------------------------------------------------
ThyPRO-39 Overall QoL-impact scale (QoL39)
*-------------------------------------------------------------------------------------------;
QoL39 =tq12*25;

Label QoL39 = 'ThyPRO-39 Overall QoL-impact Scale';


*-------------------------------------------------------------------------------------------
ThyPRO-39 Composite scale (Composite)
*-------------------------------------------------------------------------------------------;
if n (of TQ2A TQ2C TQ3B TQ4A TQ4B TQ4F TQ5B TQ5C TQ5E TQ6A TQ6E TQ6G TQ7C TQ7D
TQ7H TQ8A TQ8B TQ8C TQ9A TQ9C TQ9E TQ12) gt 10 then

Composite=100*(mean(TQ2A, TQ2C, 4-TQ3B, TQ4A, TQ4B, TQ4F, TQ5B, TQ5C, TQ5E,TQ6A, TQ6E,
4-TQ6G, TQ7C, TQ7D, 4-TQ7H, TQ8A, TQ8B, TQ8C, TQ9A, TQ9C, TQ9E, TQ12))/4;

Label Composite = 'ThyPRO-39 Composite QoL Scale';
```